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Total Synthesis of Phorboxazole A via *de Novo* Oxazole Formation: Strategy and Component Assembly

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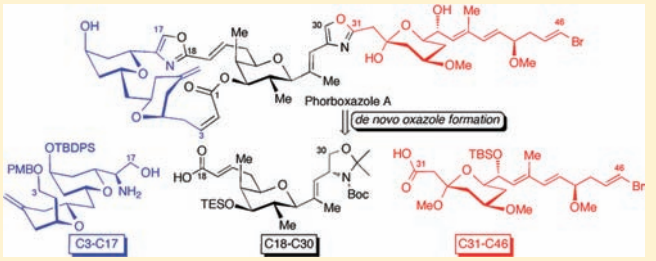
Supporting Information

ABSTRACT: The phorboxazole natural products are among the most potent inhibitors of cancer cell division, but they are essentially unavailable from natural sources at present. Laboratory syntheses based upon tri-component fragment coupling strategies have been developed that provide phorboxazole A and analogues in a reliable manner and with unprecedented efficiency. This has been orchestrated to occur via the sequential *or simultaneous* formation of both of the natural product's oxazole moieties from two serine-derived amides, involving oxidation−cyclodehydrations. The optimized preparation of three pre-assembled components, representing carbons 3−17, 18−30, and 31−46, has been developed. This article details the design and syntheses of these three essential building blocks. The convergent coupling approach is designed to facilitate the incorporation of structural changes within each component to generate unnatural analogues, targeting those with enhanced therapeutic potential and efficacy.



BACKGROUND AND INTRODUCTION

Natural products continue to provide novel lead molecules for probing fundamental biological processes and the development of therapeutic agents to treat human diseases. Gaining reliable access to biosynthetic lead compounds that are limited in availability and structural diversity is often key in advancing these goals. For this, laboratory synthesis is often enabling. In turn, the design and implementation of effective strategies for the *de novo* assembly of complex molecules may benefit from biosynthetic considerations. As a case in point, the biosynthetic convergence of non-ribosomal peptide and polyketide synthase pathways gives rise to structurally novel and biologically active natural products that embody remnants of linearly fused amino acids and ketide units.[1] Among the many striking examples of such merged biogenesis are the marine-derived phorboxazole natural products (**1** and **2**, Scheme 1).[2]

The phorboxazoles were separately isolated from extracts of sponges *Phorbas* sp.[2] and *Raspailia* sp.[3] collected off western Australia in the 1990s by Molinski and Capon, respectively. The phorboxazoles were originally reported to exhibit potent S-phase cytostatic activity against cancer cell lines with unique, yet unknown modes of action.[2a,2b] As such, the phorboxazoles represent singular anti-cancer leads. The ultimate biogenetic source of the phorboxazoles remains unknown, and isolation in substantial quantities from natural sources is currently untenable. It seems likely that the phorboxazoles are biosynthesized by a symbiotic marine microorganism, given that the known sources of non-ribosomally biosynthesized peptides are generally bacteria and fungi.

The rare natural occurrence and undefined biogenetic origin of the phorboxazoles makes laboratory synthesis the most reliable source.[4] Total synthesis can also uniquely provide more accessible non-natural analogues.[5−7] The original laboratory synthesis of a phorboxazole was reported in 1998. This work supported preliminary structure−activity studies that indicated both intact oxazole rings are required, whereas only minor structural changes are tolerated in maintaining potent cytostatic activity. For example, the C45,C46 terminal alkyne[5a,7a,7c] serves as an active[6,7a,7c] and useful[8] surrogate for the terminal vinyl bromide of **1**.

The first-generation total synthesis of phorboxazole A featured the strategic disconnection of the target into three fragments of comparable size and complexity. These were joined via *de novo* formation of both oxazole moieties from serine-derived amides and an intramolecular Still−Gennari reaction. Among the total syntheses of phorboxazoles, only the original has employed fragment couplings based upon the biomimetic amidation−cyclodehydrative oxazole formation process. At the outset, literature precedents provided no assurance that serine-derived oxazoles could be assembled efficiently within the framework of such complex intermediates.[9,10] In contrast, variations of the intramolecular Still−Gennari process[11] first used to form the natural products' C1−C3 (*Z*)-acrylate moiety have almost universally been adopted in subsequent total syntheses.[4e]

The C29−C31 oxazole moiety of phorboxazole A was first disconnected into a C1−C30 macrolide bearing a C29−C30

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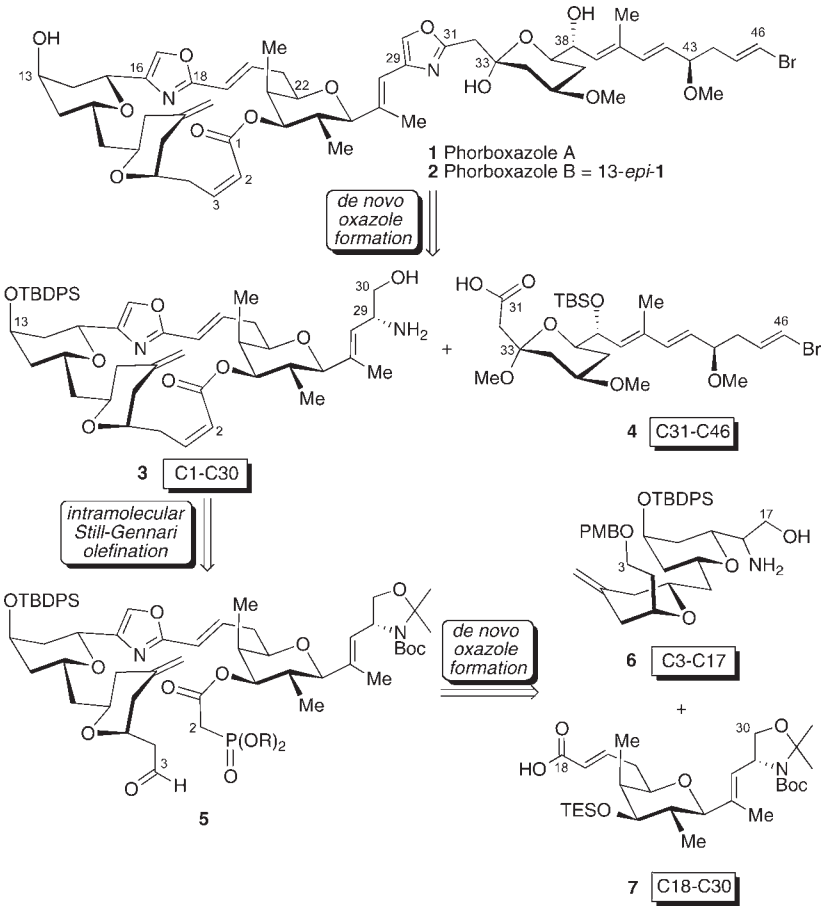
Scheme 1. Original Retrosynthetic Dissection of the Phorboxazoles



vicinal amino alcohol (**3**) and the C31−C46 carboxylic acid **4** (Scheme 1). Notably, these advanced intermediates embody all of the functionality required to complete the total synthesis, yet they contain only three protecting groups combined — silyl ethers at the C13 and C38 positions and a ketal at C33. The macrolide containing intermediate **3** was disconnected into phosphonate−aldehyde **5**, which in turn could arise from another *de novo* oxazole assembly from component vicinal amino alcohol **6** and carboxylic acid **7** partners. Thus, the three fragments representing C3−C17 (**6**), C18−C30 (**7**), and C31−C46 (**4**) of phorboxazole A were targeted as the initial key building blocks, and their syntheses were originally published in 1997,[12a] 1996,[12b] and 1998,[12c] respectively. This tri-component approach was designed to provide flexible access to the phorboxazoles as well as synthetic analogues. As a prelude to examining the key fragment coupling methods — oxazole and (*Z*)-acrylate formation — the stereoselective and preparative-scale syntheses of the individual building blocks were required. This article details the evolution of the syntheses of each component **4**, **6**, and **7** of phorboxazole A, culminating in robust and reliable preparations of each, which in turn have supported efficient synthesis of the natural product and structural analogues.

RESULTS AND DISCUSSION

1. Synthesis of the C3−C17 Domain. The C3−C17 synthetic fragment **6** contains a methylene-linked bis-oxane moiety terminally substituted with C16,17 vicinal amino alcohol and C3 aldehyde precursor functionalities. Interestingly, while both oxanes of the C5−C15 portion of the phorboxazoles adopt chair conformations, each is stereochemically differentiated in a 1,3-sense across the bridging ether oxygens. The C5−C9 oxane is *trans*-substituted in that it exhibits an axial branch at C5 and equatorial substitution at C9, whereas the C11−C15 ring is diequatorially *cis*-substituted at C11 and C15. The intervening polyketide carbonyl-derived functionalities at C7 and C13 within each oxane ring are also differentially functionalized as a C7 *exo*-methylene and an alcohol at C13, the configuration of which distinguishes phorboxazole A from B. Thus, although tetrahydropyranone intermediates would provide access to each of the differently substituted oxane moieties within **6**, the *trans* axial−equatorial versus *cis* diequatorial substitution necessitated divergent processes to assemble each of the cyclic ethers. Given the potential stereochemical-directing influence of the C16 stereogenic center in an α-substituted C15−C17 aldehyde and the potential for 1,3-stereochemical induction from C11 to C9, we were immediately attracted to sequential hetero-Diels−Alder (HDA) assemblies of the C11−C15 and C5−C9 oxanes. Thus, intermediate **6** could derive via methylenation of a C7 ketone **8**, which in turn would ideally arise from an *exo*-selective HDA reaction between the Cink diene **10**[12a] and a C9−C17 aldehyde **9** (Scheme 2). We considered whether 1,3-stereochemical induction from the C11 oxane stereogenic center could be expected to establish the correct relative stereochemistry about

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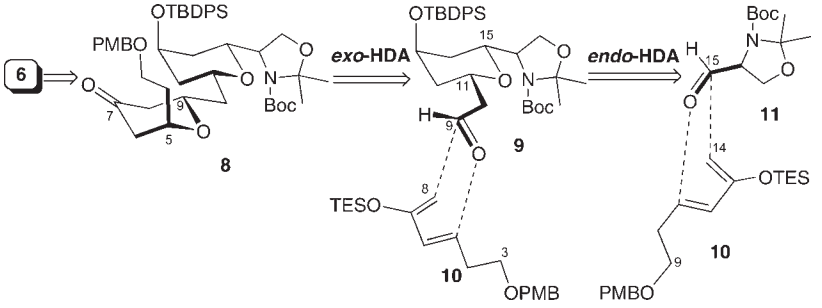
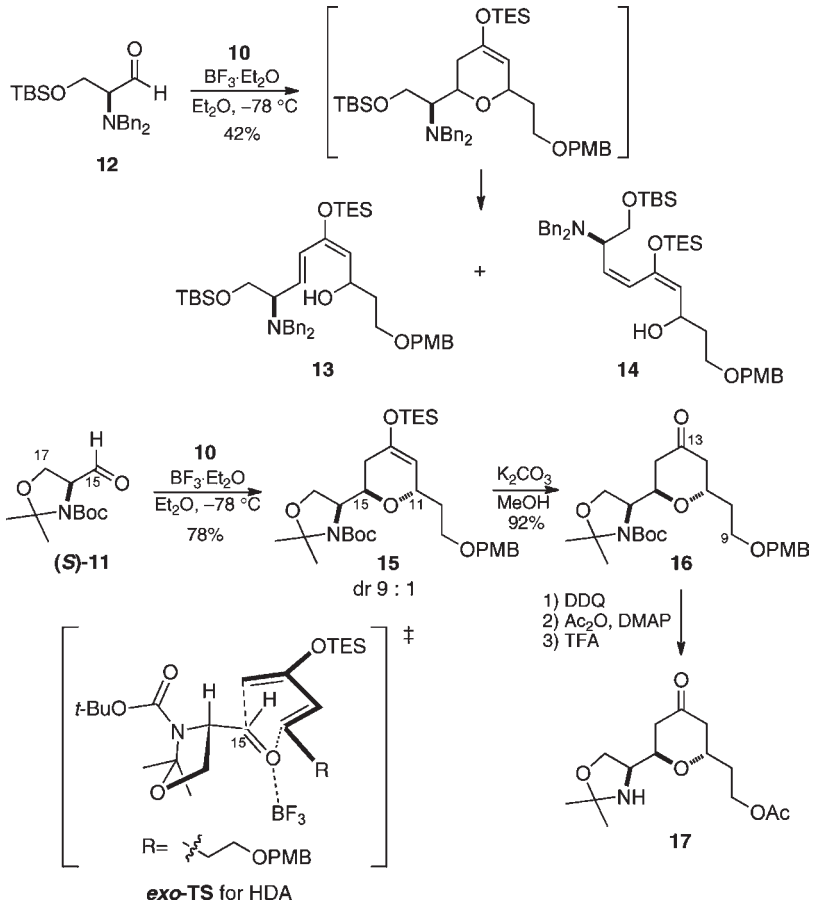
Scheme 2. Iterative HDA Plan for the Assembly of the C3−C17 Domain



Scheme 3. Reactions of Cink Diene 10 with Reetz's and Garner's Aldehydes



the C5−C9 HDA adduct. Also the diene **10** was envisioned to be employed iteratively for the assembly of **9** via an initial *endo*-HDA reaction with an α-amino aldehyde such as **11**[13] by 1,2-stereochemical induction.

1.1. Initial HDA Approach to the C11−C15 Oxane. Several iterations on the assembly of the C3−C17 domain utilizing HDA chemistry have evolved in our studies. The first involved a comparison of Reetz's (**12**)[14] and Garner's (**11**)[13] aldehydes with glyceraldehyde acetonide and **10** (Scheme 3) to form the substituted C11−C15 oxane.[15] The aim was to discern the utility of each aldehyde and diene pair in terms of cycloadduct yields and diastereoselectivities.

Attempts at HDA reactions between diene **10** and **11**, and **10** and **12**, under the influence of $BF_3 \cdot Et_2O$ in Et_2O[16] gave interesting results. The reaction between **10** and **12** gave products **13** and **14**, apparently arising from an HDA reaction followed by elimination to open the oxane ring. In contrast, the HDA reaction between **10** and **11** gave two silyl enol ether products (**15a,b**), isolated in a 9:1 ratio (Scheme 3).[17] The product mixture was converted into the corresponding ketones, and the major diastereomer **16** was separated and analyzed. After conversion of PMB ether **16** into acetate **17**, analysis by ^{1}H NMR spectroscopy (50 °C) showed that the coupling constants between the four α-keto protons and the two β-methine protons are 10, 6.5, 4.5, and 4 Hz, consistent with a C11−C15 *trans*-substituted oxane.[15] A *cis*-substituted oxane would be expected to have two coupling constants greater than 10 Hz each. These results indicated that the major diastereomer was formed from an

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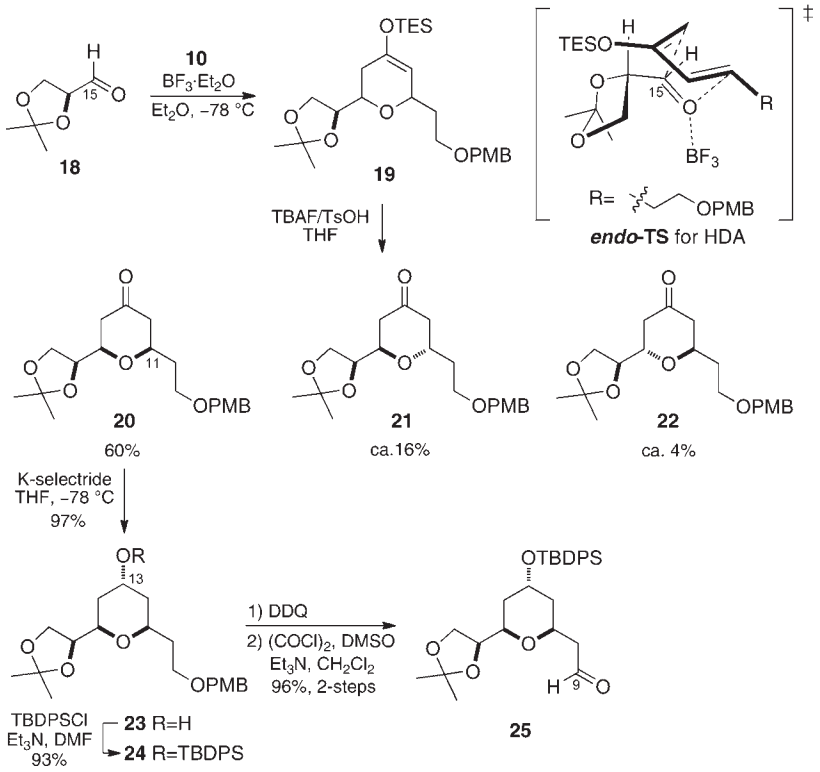
Scheme 4. HDA Reaction of Cink Diene 10 with Glyceraldehyde Acetonide



exo-HDA reaction, likely due to the combined steric hindrance by the *N*-Boc moiety and the methyl groups of the acetonide to deter *endo* approach of the diene. The assignment of the relative configuration of the C15−C16 stereochemistry in **17** was based on previous cyclocondensation reactions with Garner's aldehyde.[13a] The preliminary results favoring *trans*-C11,C15-substituted HDA products with **11** prompted the adoption of an α-alkoxy aldehyde for the HDA reaction and deferring the installation of the C16 nitrogen until a later stage.

Next, (*S*)-glyceraldehyde acetonide **18** was used as a starting point for carbons 15−17 of the phorboxazoles. Danishefsky reported that cyclocondensation reactions with glyceraldehyde acetonide were highly Cram-selective and that no racemization was detected.[18] We found that the HDA reaction between (*S*)-glyceraldehyde acetonide (**18**) and diene **10** proceeded smoothly under $BF_3 \cdot Et_2O$ catalysis (Scheme 4). This provided the C11−C15 dihydropyrans **19** in over 80% yield with desired stereochemistry as the major diastereomer in a 16:4:1 mixture. This presumably arose via an *endo*-Cram transition state, such as that illustrated (**19** ***endo*-TS**, Scheme 4). The silyl enol ethers were converted into their corresponding ketones (**20**−**22**) to facilitate separation. The major diastereomer (**20**) was isolated in 60% overall yield from diene **10**. The C11,C15 *cis* and *trans* substitutions of the diastereomers were determined from the ^{1}H NMR coupling constants of the α-keto/*β*-methine protons. The two minor diastereomers (**21**, **22**) were both *trans*-substituted, consistent with an *exo* approach of the diene.

For compound **21**, the vicinal coupling constants between the four α-keto protons and the two *β*-methine protons are 6.5, 6.5, 5, and 5 Hz. For isomer **22**, the corresponding vicinal coupling constants are 8, 5.5, 5.5, and 5 Hz.[15] Diastereomer **21** was formed in greater amount, presumably due to the previously observed Cram selectivity of cycloadditions with glyceraldehyde acetonide. Attempts at increasing the *endo* selectivity of the HDA reaction between **10** and **18** by lowering the reaction temperature to −100 °C or switching the solvent to toluene were unsuccessful. Thus, attention was turned to converting ketone **20** into a C9 aldehyde as a prelude to a second HDA reaction to form the C5−C9 oxane. Reduction of **20** with potassium tri-*sec*-butylborohydride provided the desired axial alcohol **23**. Alternatively, the corresponding equatorial C13 alcohol corresponding to phorboxazole B was also prepared using sodium borohydride.[19] Thus, this approach was equally useful to formally access either of the phorboxazoles. Alcohol **23** was protected in DMF as TBDPS ether **24** before the PMB group was removed, and the resultant primary alcohol was oxidized to aldehyde **25**.

1.2. Initial Studies on the HDA Approach to the C5−C9 Oxane. The first attempts to iteratively use the Cink diene **10** for successive HDA assemblies of the bis-oxane domain involved the use of C9 aldehyde **25** under $BF_3 \cdot Et_2O$ catalysis (Scheme 5).[15] This gave all four possible cycoadduct isomers of **26** in a 6:3:3:2 ratio and 68% combined yield. Attempted use of $TiCl_4$, Ti(*i*-OPr)$_4$, or $LiClO_4$ for the reaction of **10** and **25** gave no appreciable cycloadducts. At this stage, a more stepwise process was pursued, beginning with the simpler Kitihara−Danishefsky diene (**27**).[18] This involved an initial HDA reaction between **25** and **27**[18] catalyzed by $TiCl_4$ in THF, which produced pyranone **28** in 74% yield as an 8:1 ratio of diastereomers (Scheme 5). Treatment of **28** with a simple silyl ketene acetal[20] under $LiClO_4$ catalysis produced the silyl enol ether **29** in 85% yield. Conjugate additions upon dihydropyranones with silyl ketene acetals under $LiClO_4$ catalysis are known to proceed with high *trans* selectivity.[21] This was confirmed in the present case via X-ray crystallographic analysis of **29** (Figure 1).

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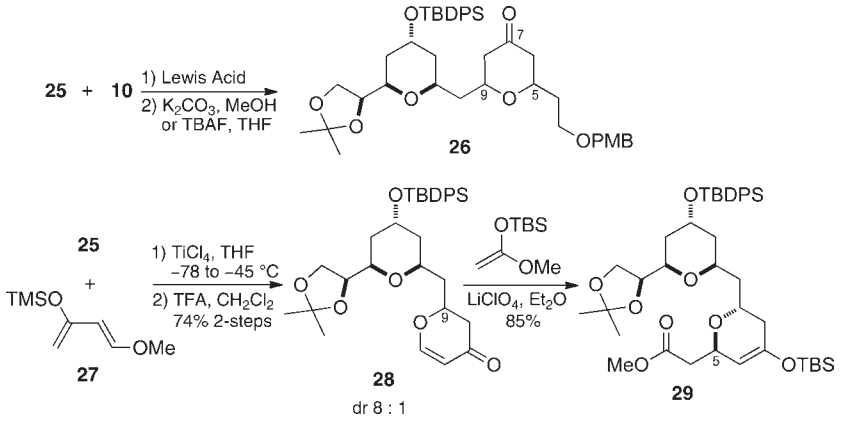
Scheme 5. Initial Attempts on the HDA Approach to the C5−C9 Oxane



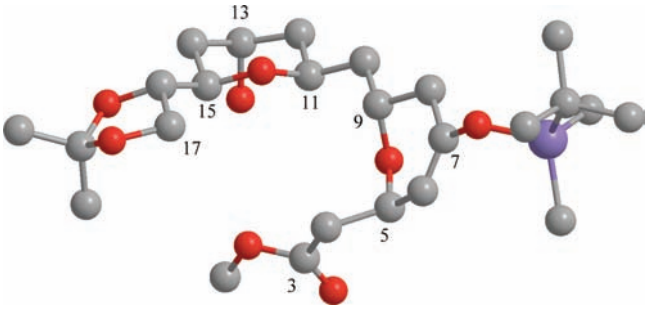


Figure 1. X-ray structure of compound **29**. The C13-OTBDPS group is omitted for clarity.

The X-ray analysis showed that the C5−C9 oxane had the anticipated *trans* substitution at C5 and C9, with the C5 and C9 substituents axially and equatorially disposed, respectively. However, the 1,3-stereochemical relationship between the C9 and C11 stereogenic centers was *anti* instead of the required *syn*. This indicated that the HDA reaction between C9 aldehyde **25** and diene **27** yielded the undesired configuration at C9 of dihydropyranone **28**. The subsequent conjugate addition occurred with the expected C5−C9 *anti* orientation, but the absolute stereochemistry at C9 was opposite to that which was desired. Thus, reversing the stereoselectivity of the HDA reaction should give, after conjugate addition, the C5−C9 oxane with the phorboxazole stereochemistry. In an effort to reverse the stereoselectivity of the reaction between aldehyde **25** and diene **27**, a variety of Lewis acids were examined in varying solvents and temperatures. However, none of the conditions surveyed provided good yields or better than 3:2 desired diastereoselectivity.

1.3. Allylic Addition−Etherification Approach to the C5−C9 Oxane and Completion of the First-Generation Synthesis of the C3−C17 Domain. The results of the cyclocondensation reactions indicated that additions to C9 β-oxanyl aldehyde **25** generated predominately the relative configuration at C9 that was opposite to that in the phorboxazoles. To take advantage of this finding, a convergent allylic addition/inversion approach was developed. This approach involves the addition of an allylic nucleophile representing C3−C8 to aldehyde **25**. The addition was expected to favor the production of an *anti* relationship between the C9 and C11 oxygen atoms, similar to the HDA reactions. The configuration at C9 would subsequently be inverted by an intramolecular etherification, in which the C9 hydroxyl is converted into a leaving group and then displaced by a C5 alkoxide, forming the C5−C9 oxane. The advantages to this approach are the convergency of adding six carbons (C3−C8) in one step and having better control of the stereochemistry, with the configuration of the C5 hydroxyl being preset.

As shown in Scheme 6, the allylic nucleophiles (**30**) initially under consideration were the silane, stannane, and bromide. The silane and stannane would be used under Lewis acid catalysis, similar to the HDA reaction. The bromide would be used via alternative organometallic processes, including a Nozaki−Hiyama−Kishi (NHK) coupling.[22] To prescreen the three potential nucleophiles, a few model reactions between aldehyde **25** and simple allylic nucleophiles were executed. The Hosomi−Sakurai reaction[23] with allyltrimethylsilane was found to be too sluggish. The reaction between **25** and allyltributyltin[24] was faster but required a large excess of the stannane to achieve an acceptable reaction rate. The NHK coupling was considered the best option at this stage. This necessitated the preparation of the allylic bromide.

The synthesis of the C3−C8 allylic bromide is shown in Scheme 7 and begins with the known alcohol-acetonide **34**,[25] derived from L-malic acid. Protection of the primary alcohol as its PMB ether followed by treatment with TsOH and methanol gave vicinal diol **35**. This was then subjected to a one-pot epoxidation−nucleophilic opening sequence[26] with the Grignard reagent derived from (2-bromo-2-propenyl)trimethylsilane[27] to afford allylic silane **36**. The hydroxyl group of **36** was protected as a TES ether to give **37**, and the silane was converted into bromide **38** upon treatment with bromine. Replacing bromine with NBS gave better yields and reproducible results on both small and large scales.

Allylic bromide **38** was coupled under NHK conditions with aldehyde **25** in 80% yield, giving a 3:2 ratio of epimeric homoallylic alcohols **31** and **39**, respectively (Scheme 7). The configurations of the newly generated secondary alcohols in **31** and **39** were determined by Mosher ester analysis,[28] which showed that the C11 oxygen substituent and the C9 hydroxyl were *anti* in **31**. The diastereomers were chromatographically separated, and the undesired epimer **39** was subjected to Mitsunobu[29] inversion to give a transient *p*-nitrobenzoate that was saponified to provide **31**. The convergency of the approach and the ease of the Mitsunobu interconversion helped to compensate for the low stereoselectivity of the coupling.

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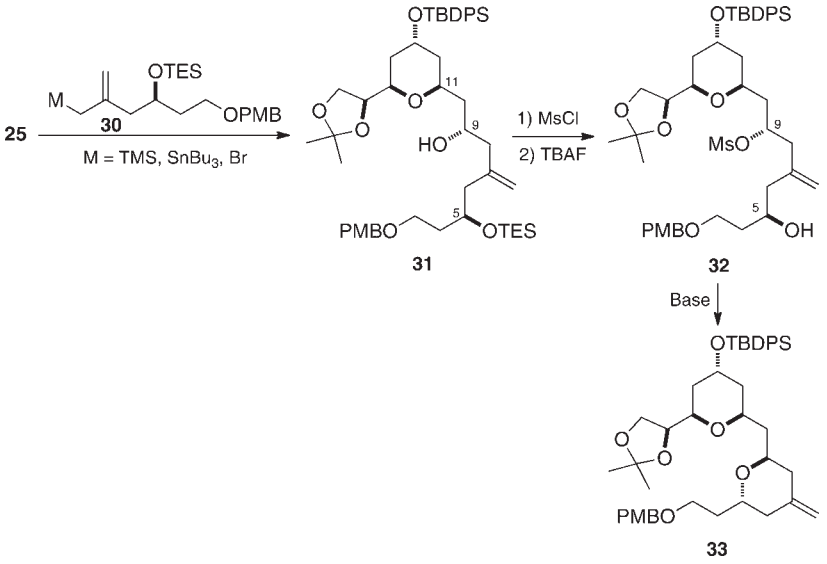
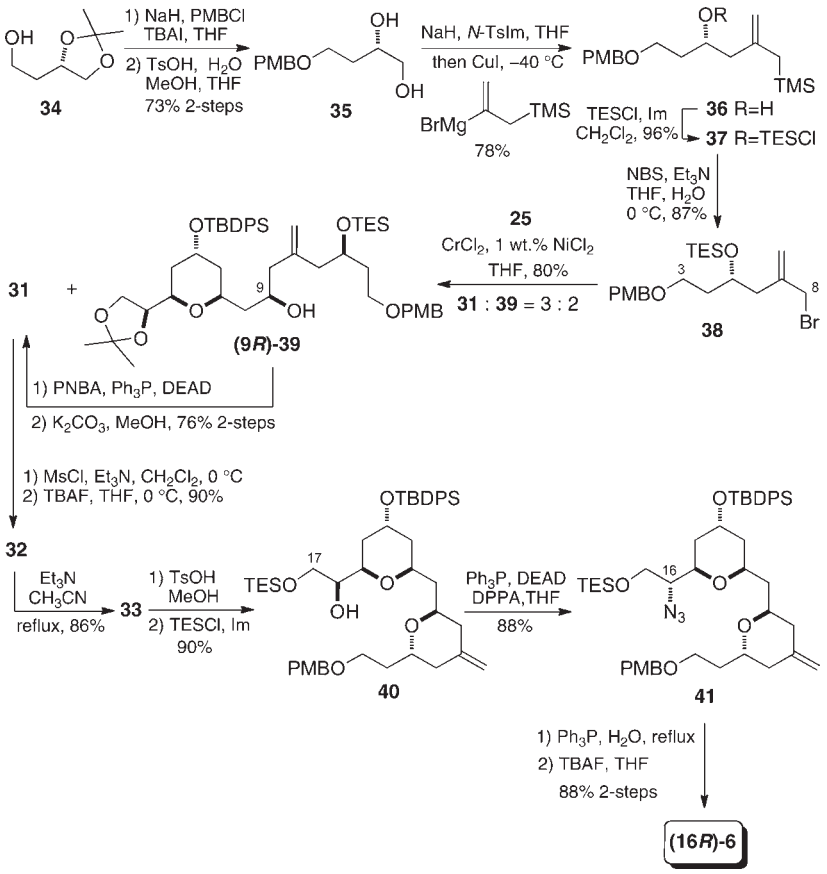
Scheme 6. Convergent Allylic Addition and Intramolecular Etherification



Scheme 7. Completion of the First-Generation Synthesis of the C3−C17 Amino Alcohol 6



The C9 hydroxyl of **31** was converted into the corresponding methanesulfonate ester, and the C5 TES ether was selectively cleaved with TBAF. The resulting C5 alcohol, C9 mesylate **32**, was subjected to intramolecular etherification attempts to form the C5−C9 oxane. The use of strong bases, such as NaH and KHMDS, gave low yields and led to considerable elimination of the mesylate to give a conjugated diene. Use of the milder base triethylamine in acetonitrile at reflux led to clean cyclization to give exclusivly the *trans*-substituted C5−C9 oxane **33** in 86% yield.

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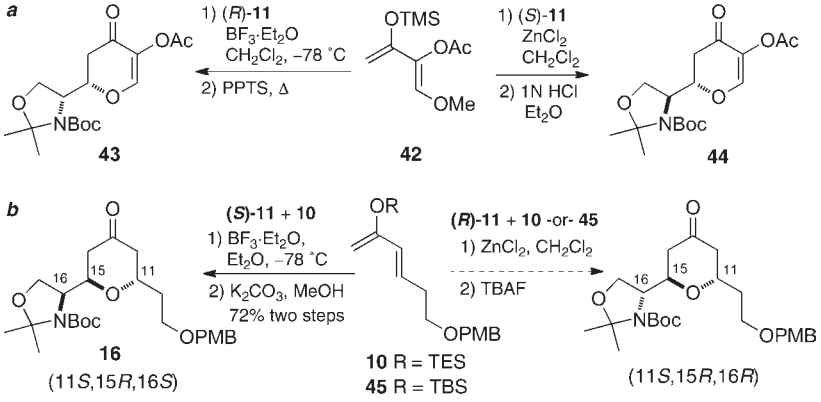
Scheme 8. Stereoselectivity Tunable HDA Reaction of Garner's Aldehyde



With the successful synthesis of bisoxane **33**, the only remaining task for completion of the C3−C17 fragment was the installation of the C16 nitrogen. Attempts to install the nitrogen via reductive amination of a C16 ketone were low yielding and caused C15 epimerization. Alternatively, the diol obtained by removal of the acetonide was selectively protected to give secondary alcohol **40**, which was subjected to a Mitsunobu-type displacement with diphenylphosphoryl azide[30] (DPPA), yielding azide **41**. The reduction of the azide was accomplished with triphenylphosphine and water[31] to produce amine **6** after C17 silyl ether cleavage. The synthesis of amino alcohol **6** represents the completion of the first-generation synthesis of the C3−C17 fragment. It required 17 steps and produced **6** in ca. 10% overall yield from 3-(*p*-methoxybenzyloxy)propanal.[12a] The key aspects of the synthesis are the HDA reaction to form the C11−C15 oxane and the intramolecular etherification reaction to form the C5−C9 oxane.

1.4. Iterative HDA Approach to the C3−C17 Domain. Although the original synthesis of the C3−C17 domain **6** did contribute to the first total synthesis of **1** and a few informative analogues, its shortcomings include the late-stage, multistep incorporation of the requisite C16 amino group. Further processes en route to **6** included ineffective attempts to simultaneously incorporate both the C3−C8 side chain and the desired C9 configuration and the multistep liberation and use of the C5 hydroxyl group to close the C5−C9 oxane. Therefore, a more streamlined approach was desired for the rapid access to **6**.

The use of Garner's aldehyde **11** and diene **10** had allowed the early incorporation of the necessary C16 nitrogen atom, but it favored the generation of the *trans*-C11,C15-substituted HDA product **15** (Scheme 3), whereas a *cis* orientation is required. It was reasoned that the relative configuration at C11 of a Garner's aldehyde cycloadduct could be adjusted via a β-elimination/hetero-Michael addition equilibration process at the stage of a C9 aldehyde. Indeed, this type of thermodynamic equilibration was used to establish the C22,C26 diequatorially substituted oxane in the first publication of synthetic studies toward the phorboxazoles.[12b] Thus, we re-examined the utility of Garner's aldehyde for priming our planned iterative HDA approach to assemble the C3−C17 phorboxazole intermediate **6**.

Published studies on the HDA reactions of Garner's aldehyde **11** with doubly activated diene **41** indicated that bidentate Lewis acids such as $ZnCl_2$ afford the *threo* diastereomer **44**, while the monodentate Lewis acid $BF_3\cdot Et_2O$ yielded the *eythro* product **43** (Scheme 8a).[13a,32] Accordingly, the initially prepared major HDA adduct between (*S*)-**11** and diene **10** using $BF_3\cdot Et_2O$ (**15**, Scheme 3) was assigned the (11*S*,15*R*,16*S*)-stereochemistry. This implied that a $ZnCl_2$-mediated HDA reaction of (*R*)-**11** with the diene **10** should give a cycloadduct that has the (11*S*,15*R*,16*R*)-stereochemistry (Scheme 8b).

To secure firm empirical evidence for the predicted stereoselectivity, (*R*)-**11** was premixed with $ZnCl_2$, followed by addition of the more stable TBS variant of the Cink diene **10**. The OTBS-substituted diene **45** proved to be sufficiently stable to the $ZnCl_2$ reaction conditions, whereas **10** was not. The cycloaddition proceeded with high diastereoselectivity and efficiency to afford a silyl enol ether product **47**, which was converted to ketone **46** after treatment *in situ* with TBAF (Scheme 9). Fortunately, ketone **46** could be crystallized from pentane−ether (2:1, v/v). X-ray crystallographic analysis of **46** (Figure 2) determined that the stereochemistry was (11*S*,15*R*,16*R*) as anticipated.[33] The C11,C15 *trans*-oxane **46** was obtained presumably through an *exo* cycloaddition transition state. These results suggest that the desired (11*R*,15*R*)-stereochemistry of the phorboxazoles could be obtained by using either a combination of (*R*)-Garner's aldehyde and bidentate Lewis acid ($ZnCl_2$) or a combination of (*S*)-Garner's aldehyde and monodentate Lewis acid ($BF_3\cdot Et_2O$) (Scheme 8), and the former gave higher diastereoselectivity. However, the C11 stereogenic center would need to be adjusted post-cycloaddition to afford the corresponding *cis*-oxane in either case.

These results supported the synthetic plan illustrated in Scheme 2. This involved an iterative HDA process to construct the two oxanes from commercially available Garner's aldehyde **11** and the diene **45**. The latter would provide both the C3−C8 and C9−C14 backbone carbons of **1**. The 2,6-*cis* relationship of the C11−C15 oxane could be generated in an *exo*-selective HDA reaction with Garner's aldehyde followed by a base-induced epimerization at C11 at the stage of a C9 aldehyde. The 2,6-*anti* C5−C9 oxane would subsequently be obtained in an *exo*-selective HDA reaction with a Lewis acid that takes advantage of a bidentate chelation of the oxygen atom lone pairs of electrons in the C9 aldehyde and the C11−C15 oxane ring.

The ketone **46** was reduced with K-Selectride to give an axial alcohol **48**, which was protected as a TBDPS ether **49**. Cleavage of the PMB ether in **49** followed by oxidation of the resultant primary alcohol provided aldehyde **50**, with the undesired (11*S*)-configuration. After considerable optimization, it was found that

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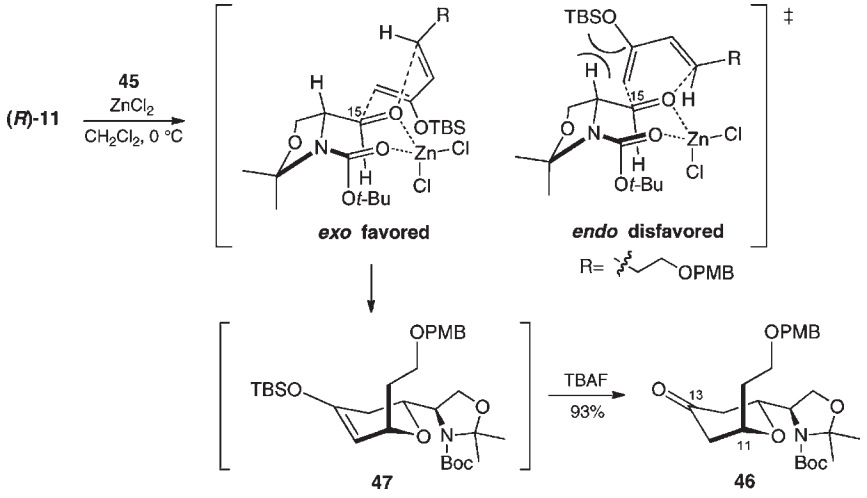
Scheme 9. $ZnCl_2$-Mediated *Exo*-Selective HDA Approach to the C11−C15 Oxane



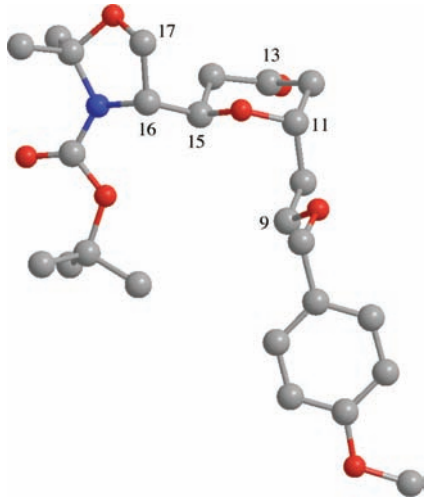


Figure 2. X-ray structure of **46**.

this β-*trans*-oxanyl aldehyde could be epimerized efficiently in large scale (ca. 60 g) to the diequatorially *cis*-substituted oxane **9** using catalytic DBU in benzene at reflux (Scheme 10). The diequatorial orientation of the C11 and C15 substituents of **9** was corroborated by the observance of an NOE between the C11 and C15 methine protons. This was further demonstrated via X-ray crystallography of a C1−C30 synthetic intermediate. Hence, the desired C11−C17 intermediate *with the C6 nitrogen pre-installed* was obtained readily on a large scale from commercially available materials. The next challenge was to achieve 1,3-stereochemical induction using the β-oxanyl-aldehyde's C11 stereogenic center to establish the configuration at C9 in a second HDA process using the same diene **45**.

A survey of various Lewis acids ($SnCl_4$, $TiCl_4$, $TiCl_2(Ot\text{-}Bu)_2$, $MgBr_2 \cdot Et_2O$, and ZnI_2) and solvents for the cycloaddition between aldehyde **9** and diene **45** determined that ZnI_2 in CH_2Cl_2 was optimal. It was expected that an *exo*-selective HDA process would predominate due to the steric hindrance of the Zn-chelated β-oxanyl aldehyde (Scheme 10). In the event, **9** was pre-mixed with 1 equiv of ZnI_2 in CH_2Cl_2 for 20 min at 0 °C before diene **45** was added as a solution in CH_2Cl_2. This provided a mixture of TBS silyl enol ether cycloadducts that were subjected together to treatment with TBAF to convert them into the corresponding ketones while retaining the TBDPS ethers. This afforded one major ketone isomer **8** along with minor adducts by TLC. Without separation, this mixture of ketones was subjected to Wittig olefination to afford the exocyclic alkenes. The major isomer **51** (obtained in 60% from **9**) was carried forward, while the minor ones were not processed further. Treatment of **51** with HCl in methanol effectively cleaved the Boc and acetonide protecting groups from the vicinal amino alcohol to give the corresponding amino alcohol. This was compared with (16*R*)-**6** (Scheme 7), which was previously prepared from glyceraldehyde acetonide, and found to be spectroscopically and chromatographically identical.

In summary, this second-generation approach allows rapid access to the C3−C17 fragment **6** of phorboxazole A in ca. 30% yield over 11 steps from known intermediates Garner's aldehyde (*R*)-**11** and 3-(*p*-methoxybenzyloxy)propanal.[34] It is highlighted by the iterative HDA strategy and a retro-hetero-Michael/hetero-Michael equilibration for the stereocontrolled synthesis of the methylene-linked bis-oxane. This greatly enhanced the diastereoselectivity of C8−C9 bond formation and the efficiency of the C5−C9 oxane construction. In addition, the terminal functionality of **6** was installed at an early stage to facilitate orthogonal C16−C18 oxazole and C1−C3 acrylate formation, which necessitated access to the complementary C18−C30 intermediate.

2. Synthesis of the C18−C30 Domain. The penta-substituted C22−C26 oxane of the phorboxazoles bears four equatorial substituents and a sole axially oriented one at C23. The 1,3-diequatorial branches at C22 and C26 link the macrolide and side-chain oxazole moieties together. Thus, the fully functionalized key building block **7** was designed to incorporate a carboxylate at C18 and a masked vicinal amino alcohol moiety at C29−C30 (Scheme 11). This stereochemically dense, rather elaborate homologue of serine was targeted for multigram-scale synthesis via the establishment of the four contiguous stereogenic centers in the C20−C30 acrylate **53**. For this, a Paterson aldol addition[35] between ethyl ketone **55** and serine-derived aldehyde **54**, followed by a β-hydroxy-directed ketone reduction, was planned.[36] The closure of the oxane **52** would then be accomplished by an intramolecular hetero-Michael addition upon the C20−C22 acrylate in **53**. The desired oxane closure product would have the vicinal C22,23 stereogenic centers in a

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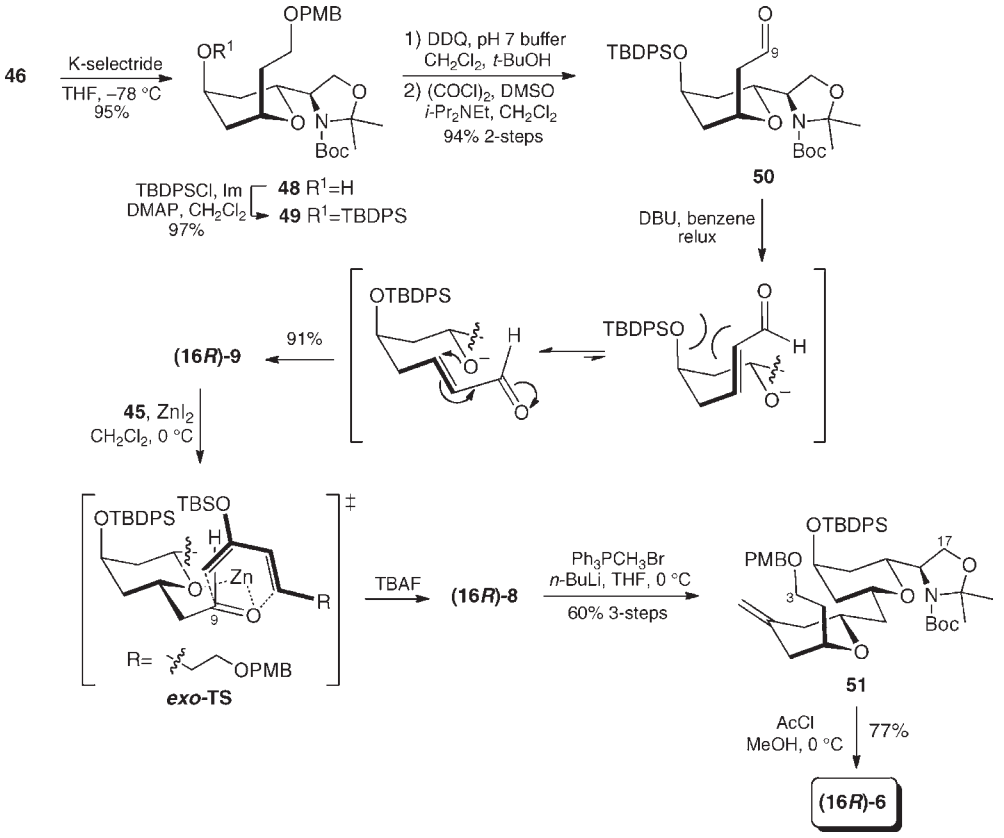
Scheme 10. Completion of the C3−C17 Domain via Iterative HDA Approach



1,2-*syn* relationship. It was recognized that the C22,C26-diequatorial substitution would be thermodynamically favored over an axial−equatorial orientation arising from hydroxy-acrylate **53** isomerization.

The cyclization stereoselectivity of intramolecular hetero-Michael additions to form modestly substituted oxanes has been studied previously. Martin and co-workers reported the effect on the relative stereochemistry of the cyclization products of the γ-stereogenic center when substituted with an electron-withdrawing benzoate under nominally kinetically controlled conditions (Scheme 12a).[37] They found that the (*E*)-acrylate, when treated with NaH in THF at 0 °C for 1 h, gave the 2,3-*cis* product as the major product. However, the selectivity was reversed when the (*Z*)-acrylate was used. Banwell and co-workers reported the effect of the ω-stereogenic center in a similar system. They reported that the (*E*)-acrylate kinetically favored the formation of the 2,6-*trans* product, but the (*Z*)-acrylate favored the 2,6-*cis* product (Scheme 12b).[38] Therefore, it was difficult to predict the kinetic diastereoselectivity of the intramolecular hetero-Michael reaction of a tetra-substituted hydroxyl acrylate (e.g., **53**) to form the C22−C26 oxane. A necessary prelude to examining the cyclization of hydroxy-acrylate **53** was its preparation.

*2.1. Synthesis of Acrylate **53** and Initial Studies on the Hetero-Michael Cyclization.* The C20−C30 acyclic acrylate **53** was prepared from C22−C25 ketone **55** and C26−C30 aldehyde **54**. The C22−C25 ketone **55** arose from (*S*)-(+)-methyl-3-hydroxy-2-methylpropionate via PMB ether formation,[39] DIBAL reduction, ethyl Grignard addition, and Swern oxidation.[40] Aldehyde **54** contains an α,β-trisubstituted alkene and a protected γ,δ-vicinal amino alcohol. The C27−C28 alkene was installed stereoselectively via olefination of Garner's aldehyde (*S*)-**11**.[13] Use of triethyl 2-phosphonopropionate **64** under Masamune−Roush conditions[41] (LiCl, DBU, or DIPEA) gave **62**/**63** in a 2:3 ratio of *E*:*Z* alkene isomers, whereas use of 1-(ethoxycarbonyl)ethylidene-triphenylphosphorane (**65**)[42] in CH_2Cl_2 gave **62**/**63** in a 10:1 ratio of *E*:*Z* isomers and 84% yield (Scheme 13). A two-step sequence of DIBAL reduction and Swern-type oxidation cleanly afforded the C26−C30 aldehyde **54**. Alternatively, the use of 1-(formyl)ethylidene-triphenylphosphorane (**66**)[43] with **11** directly gave the desired adduct **54** in 95% yield.

Paterson aldol reactions between aldehyde **54** and ethyl ketone **55** proceeded smoothly (Scheme 13). Use of Brown's dicyclohexylchloroborane[44] for enolization of **55**, presumably generating the corresponding *E*-boron enolate, followed by addition of **54** provided an optimal yield of the *anti*−*anti* aldol product **67**. The distal C29 stereogenic center in the C26−C30 aldehyde did not appear to affect the high enol borinate π-facial selectivity of the aldol addition. The β-hydroxy ketone **67** was then reduced to the *anti*-1,3-diol **68** with $Me_4NBH(OAc)_3$.[36] Bis-silylation of diol **68** using TES triflate and Et_3N followed by oxidative cleavage of the PMB ether with DDQ[45] afforded the primary alcohol **69**. Oxidation of **69** to an aldehyde with TPAP[46] and NMO followed by olefination with (methoxycarbonyl)-methylene-triphenylphosphorane in CH_3CN gave (*E*)-acrylate **70**. The corresponding (*Z*)-acrylate **71** was subsequently obtained by oxidation of **69** with Dess−Martin periodinane[47] and olefination with bis(2,2,2-trifluoroethyl) carbomethoxymethylphosphonate using Still's conditions.[11] These two acrylates (**70** and **71**) were

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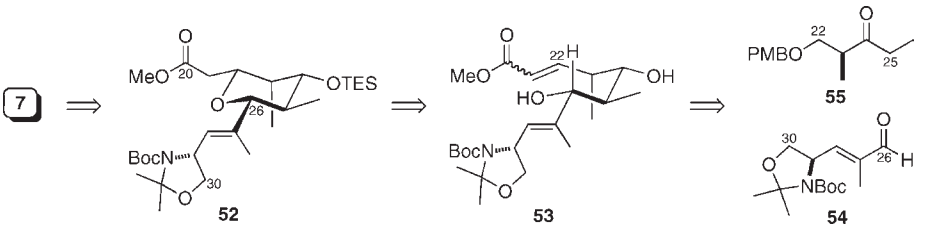
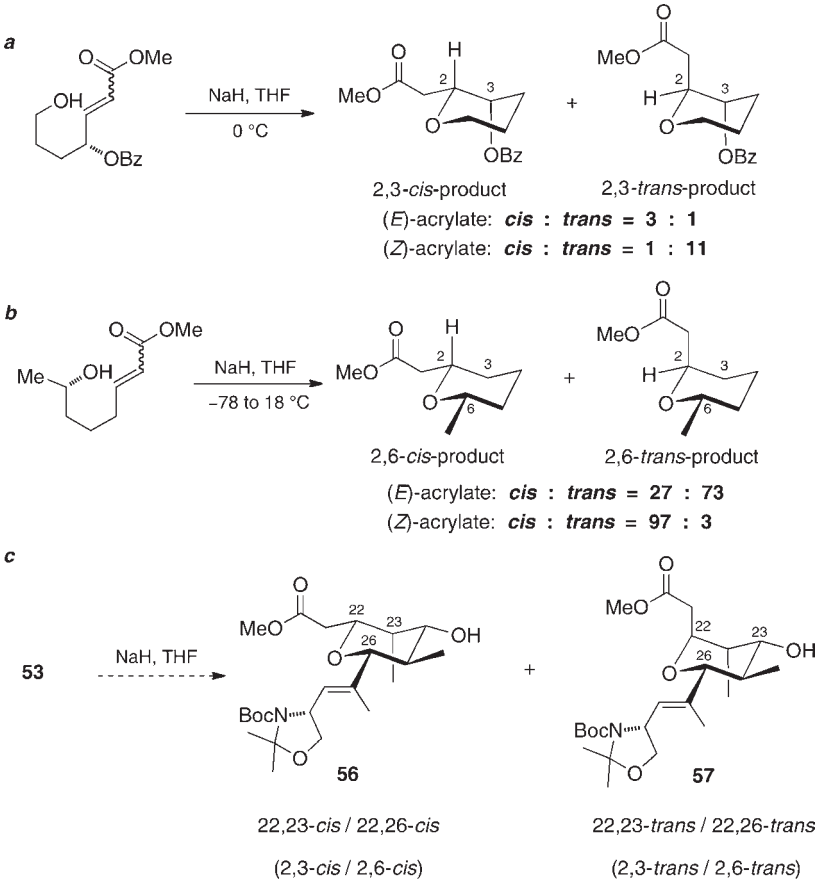
Scheme 11. Hetero-Michael/Aldol Retrosynthetic Dissection for the C18−C30 Domain



Scheme 12. Studies on *6-exo*-Hetero-Michael Cyclization



designed to study the effects of olefin geometry on the stereoselectivities of kinetic oxane formation.

The first attempt at cyclization via intramolecular hetero-Michael addition was implemented in a one-pot desilylation−cyclization approach. The C20−C30 (*E*)-acrylate **70** was treated with TBAF·H_2O in THF at room temperature for 12 h, which afforded two cyclization products, **56** and **57**, largely favoring the C22 axially substituted oxane **57** (75% combined yield, **56**:**57** = 1:7, Scheme 13). Desilylation and cyclization of the C20−C30 (*Z*)-acrylate **71** using the same conditions did not reverse the isomeric ratio but gave the same major cyclization product **57** with a similar isomeric ratio (**56**:**57** = 1:5, ^{1}H NMR spectroscopy, milligram scale). The geometry of the alkene in these acrylates did not largely affect the stereoselectivity of ring closure under these conditions. The two cyclization products **56** and **57** could be separated by simple chromatography. The major product in both cases (**57**) was crystalline and hence allowed X-ray crystallographic analysis to fully confirm its structure (Figure 3).

All attempts to obtain a suitable crystal of the minor cyclization product **56** failed, and the characterization of this compound by spectroscopic methods was complicated due to the signal broadening effects caused by rotamers of the resident carbamate moiety. To address this problem, the C24 hydroxyl of **56** was first protected as a TES ether. Subsequent ozonolysis of the olefin afforded methyl ketone **72** (Scheme 13). The relative stereochemistry of **56** was then assigned by COSY and ^{1}H NMR spectroscopic coupling constants analysis.

2.2. Inversion of the C22 Configuration and Completion of the C18−C30 Domain. It was anticipated that the kinetic ring closure product **57**, bearing the undesired C22 configuration, could be equilibrated to the thermodynamic product **56** via a retro-hetero-Michael/hetero-Michael addition process under basic conditions.

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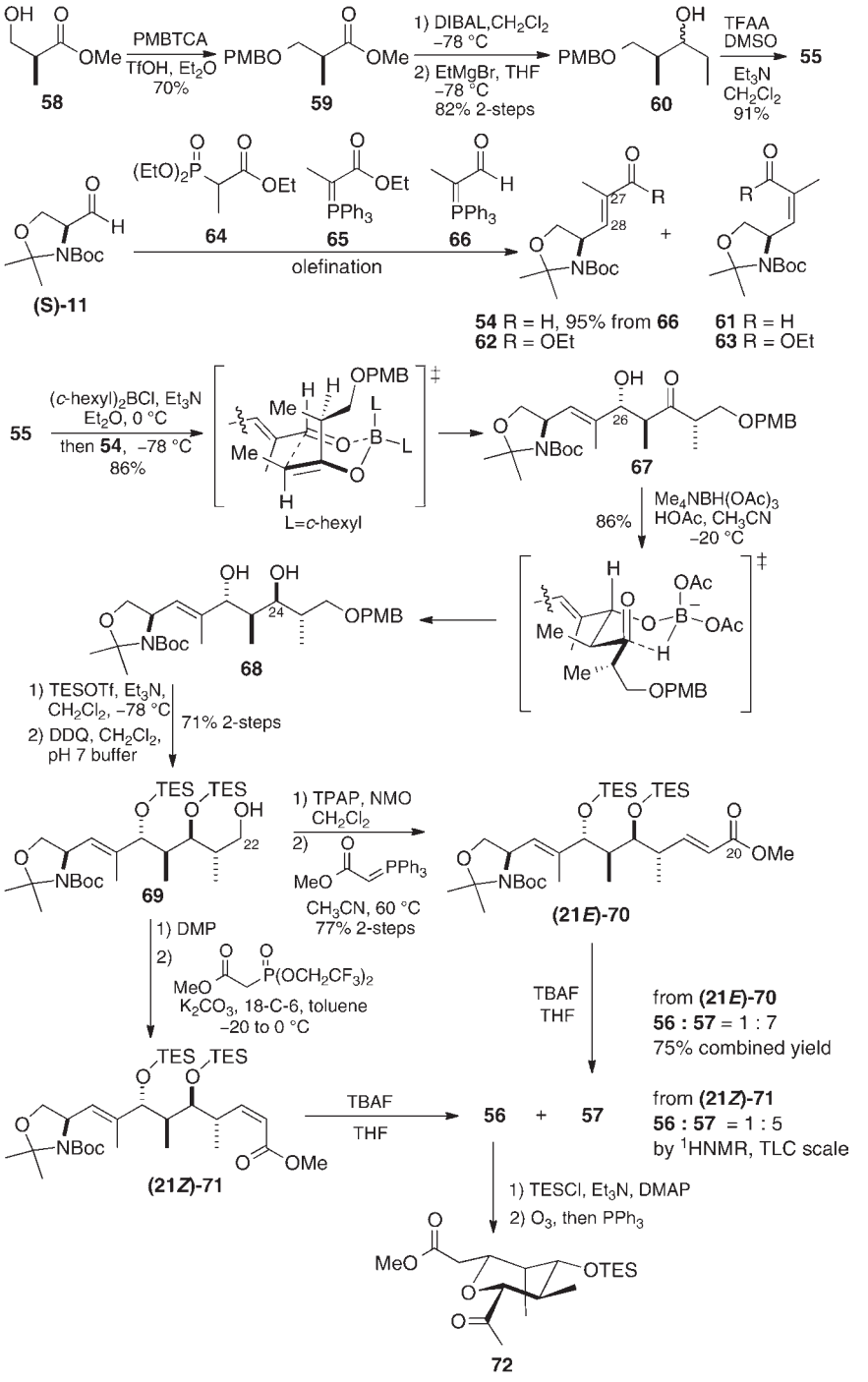
Scheme 13. Initial Attempts at the Hetero-Michael Cyclization of the Central Oxane



The first attempt to equilibrate **57** using TBAF·H_2O in THF at room temperature for 3 days changed the C22 equatorial:axial ratio to 4:1, but the yield was low (29%), presumably due to concomitant saponification of the methyl ester and epimerization at C23 (e.g., **73**, Scheme 14). The structure of the C23 methyl epimer **73** of **56** was determined by ^{1}H NMR spectroscopic coupling constant analysis (C24−H, δ 3.55 (t, J = 4.5 Hz)). A survey of equilibration conditions was undertaken to determine conditions that would suppress these undesirable side reactions.

Treatment of **57** with NaH in THF in the presence of methyl pivaloate at room temperature for 5 h provided the best initial result for C22 epimerization (56%, 9:1), but the C23 epimers of **56** and **57** both emerged as minor products. To improve the efficiency of the hetero-Michael addition reaction, a stepwise desilylation−cyclization approach was examined next. For this, desilylation of **70** with TBAF at −20 °C gave the corresponding acyclic C24,26-diol. Treating the diol with NaH in THF at 0 °C for 1 h afforded *trans*-oxane **57** as nearly the exclusive product (Scheme 14). This stepwise desilylation−cyclization gave the C22 axial product **57** in very good yield (88% for two steps), with no detectable C23 epimerization (^{1}H NMR spectroscopic analysis). Resilylation of the C24 hydroxyl in **57** afforded compound

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74, which was then submitted to thermodynamic equilibration. While the use of NaH in THF was nonproductive for this, switching to KH successfully accelerated the equilibration rate (0 °C for 1 h) and gave the desired C20,26 *cis* isomer **52** in 75% yield. This stepwise approach successfully improved the efficiency of the cyclization sequence and minimized the formation of side products.

With **52** in hand, DIBAL reduction of the methyl ester followed by olefination with (methoxycarbonyl)methylene-triphenylphorane in CH_3CN afforded the (*E*)-acrylate **75** as the only alkene isomer. Finally, saponification of the methyl ester with LiOH in aqueous THF followed by acidification with 5% HCl gave the C18−C30 fragment **7** in 84% yield, along with 10% of the desilylation product **76**. The C24 hydroxyl in **76** could be resilylated under standard conditions. Subsequent acid hydrolysis of the silyl ester at C18 provided **7** in good yield (Scheme 15).

2.3. Second-Generation Approach to the C18−C30 Domain from Evans's Oxazolidinone. In a series of attempts to shorten the overall synthetic sequence to the C18−C30 intermediate **7**, the C23−C26 stereochemical tetrad was established using Evans's chiral oxazolidinone chemistry. This involved the formation of an *E*-boron enolate from β-keto-imide **77**[48] and its addition to the C26−C30 aldehyde **54** to yield the *anti*−*anti* aldol product **78**, analogous to the *anti*−*anti* product **67** obtained from the Paterson aldol approach (Scheme 16). β-Hydroxyl-directed reduction,[36] as before, reliably provided the complete C23−C26 stereochemical array in **79**. From this intermediate, divergent paths were explored. The most ambitious was an attempted 1,6-addition to both close the central oxane ring and incorporate the complete C18−C22 fragment with the correct stereochemistry. For this, diol **79** was first converted into the bis-silyl ether **80**, the imide was reductively removed, and the resultant C22 alcohol was oxidized to aldehyde **81**. At this juncture, the aldehyde was condensed with methyl (*E*)-3-(methoxycarbonyl)-2-propenylidene-triphenylphosphorane[49] to yield dihydroxy dienoate **82** after removal of the silyl groups. Several attempts to affect the desired oxane ring closure under basic reaction conditions led to complex mixtures, with only the (*Z*)-acrylate **83** emerging as a primary identifiable product. Given these results, we turned to alternative uses of **79**.

The addition of the four-carbon side chain C18−C21 could be accomplished two carbons at a time, with intervening oxane ring formation. This involved DBU-induced δ-lactonization of diol-imide **79** followed by reduction to the cyclic hemiacetal **84** (Scheme 17). This intermediate was subjected to a one-pot conversion to methyl acrylates followed by *in situ* hetero-Michael addition to close the oxane using (methoxycarbonyl)methylidene-triphenylphosphorane and DBU in benzene at reflux. This tactic was nominally successful, but it generated a mixture of C23 as well as C22 epimers **53**, **57**, **73**, and 23-*epi*-**57**. Hence, the propensity of the axial C23 methyl group to isomerize to an equatorial orientation via dienoate intermediates once again complicated the hetero-Michael addition strategy. Taking yet another step backward, it was found that segregating the simple acrylate formation from the hetero-Michael addition process was ultimately more effective. Thus, hemiacetal **84** was condensed with (ethoxycarbonyl)methylene-triphenyl-phosphorane in the absence of exogenous base to provide dihydroxy-acrylate **70b** in 82% yield (Scheme 17). Subjection of **70b** to potassium *tert*-butoxide in THF at −50 °C gave an excellent yield of the C22,C23 *trans*-diaxial oxane **57b**, the ethyl ester analogue of methyl ester **57**. Silylation of the C24 hydroxyl in **57b** facilitated epimerization of the C22 axial stereogenic center via **74b** using KH in THF and methyl pivaloate, which gave the desired C22 equatorial product **52** in 95% yield from **74b**. Thus, the desired C22 equatorial oxane **52** was generated from acrylate **70b** in 85% combined yield. The non-enolizable methyl pivaloate was used in the equilibration process to scavenge any hydroxide in exchange for

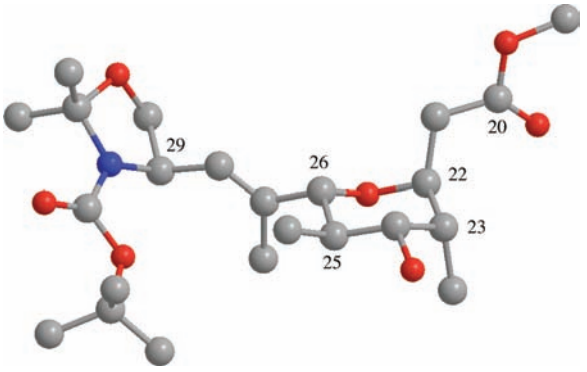
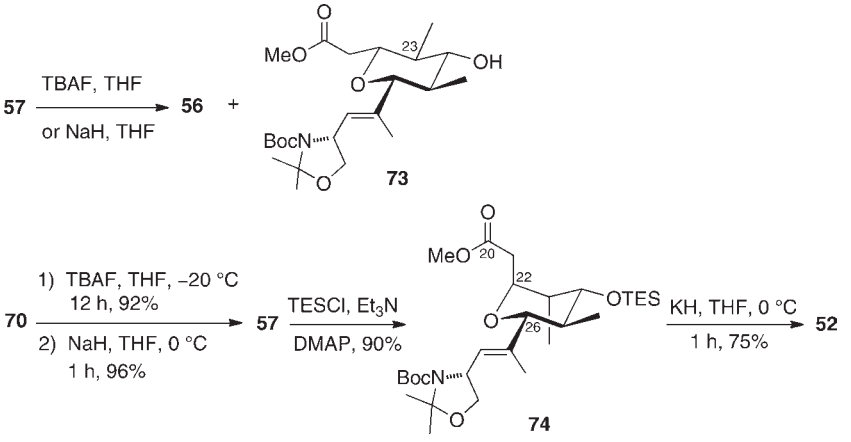


Figure 3. X-ray structure of the C22-axial product **57**.

Scheme 14. Retro-Hetero-Michael/Hetero-Michael Equilibration



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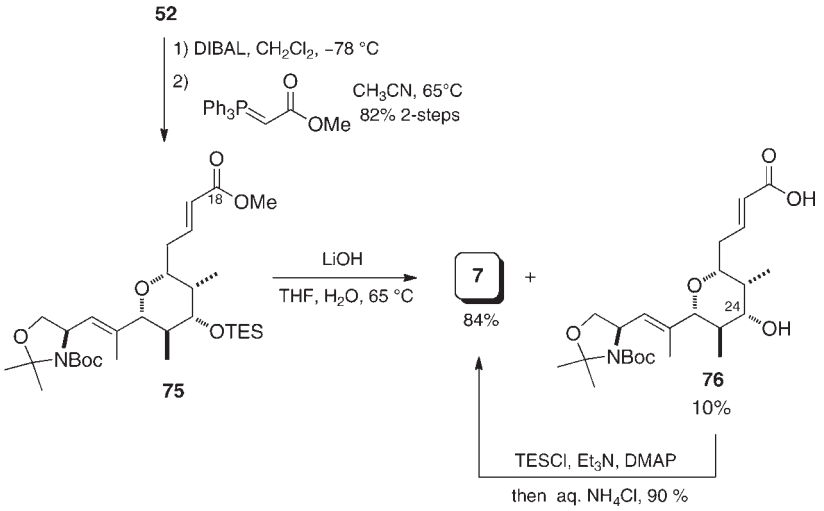
Scheme 15. Completion of the C18−C30 Carboxylic Acid 7



methoxide. Consequently, the ethyl ester of **74b** was nearly quantitatively converted into methyl ester **52**. The remaining two carbons of the C18−C30 building block **7** were installed as indicated in Scheme 15.

The ultimate synthetic route to the C18−C30 fragment thus proceeded through oxazolidinone **79**, wherein the four contiguous stereogenic centers C23−C26 were installed efficiently via an *anti*-aldol reaction using Evans's β-keto imide and substrate-directed reduction sequence. Thereafter, the C22 stereogenic center was successfully established in oxane **52** by thermodynamic equilibration. The synthesis of the C18−C30 fragment required 11 linear steps from Garner's aldehyde in ca. 31% overall yield.

3. Synthesis of the C31−46 Domain. The C31−C46 synthetic intermediate **4** (Scheme 1) embodies all of the functionality found in this portion of the natural products. This includes the C33−C37 hemiketal masked as a cyclic mixed methyl ketal, a polyene side chain terminating in an *E*-vinyl bromide, and a carboxylic acid oxidation state at C31. In addition to the C33 ketal, the C38 allylic alcohol was protected as a TBS ether to guard against oxidation during formation of the C29−C31 oxazole ring. Silicon protection of the C38 hydroxyl was designed to match that at the C13 hydroxyl, which required the more robust TBDPS group to withstand liberation of the vicinal amino alcohols under acidic conditions. Thus, only three protecting groups were required for the final fragment coupling of **3** and **4** via *de novo* oxazole formation. Thereafter, final global liberation of both C13 and C38 hydroxyls, as well as the C33 hemiketal, was envisioned to occur in one step under hydrolytic acidic conditions. The C45,46-terminal vinyl bromide would be installed by a net regio- and stereoselective hydrobromination of the corresponding alkyne **85** (Scheme 18). In addition, the terminal alkyne would serve as a simplified analogue[6] and synthetic handle for the incorporation of affinity[8a] and fluorescent groups for chemical biology studies.[8a,8c]

3.1. First-Generation NHK Coupling Approach. The first synthesis of the C31−C46 domain of the phorboxazoles was published in 1998.[12c] In designing the original synthesis of the C31−C46 intermediate **85**, it was recognized that disconnection at the C38−C39 bond might allow for a chelation-controlled addition of a C39 vinyl organometallic species, derived from iodide **86**, to the C38 aldehyde **87** to establish the correct C38 allylic alcohol configuration (Scheme 18). Adehyde **87** bears base- and acid-sensitive functionality, including an ester and its β,δ-dimethoxy substituents and the C37 α-aldehyde stereogenic center. Therefore, mild and chemoselective reaction conditions would be needed for successful C38−C39 bond formation. Although only modest Cram selectivity is generally observed in the NHK organochromium additions to aldehydes,[22,50] the exquisite chemoselectivity of this type of coupling reaction prompted us to explore it in the initial assembly of **85**. The preparation of the requisite coupling partners **86** and **87** thus became the initial experimental focus. The sole C43 stereogenic center in **86** relegated its assembly as a subordinate concern to that of aldehyde **87**. In the course of seeking reliable and scalable synthetic access to **87**, several chiral-pool-originating syntheses were developed.

The initial synthesis of the C31−C38 aldehyde **87** commenced with manipulation of D-malic acid-derived diol **88**[51] to generate aldehyde **91** (Scheme 19).[12c,52] Direct addition of methyl acetoacetate dianion to aldehyde **91** gave a 1:1 mixture of alcohols **92** in a moderate yield. Acid-promoted ketalization of **92** afforded a mixture of cyclic ketals (35*S*)-**93** and (35*R*)-**94**. Separation of the diastereomers by column chromatography allowed assignment of the newly formed stereogenic center at C35. The vicinal ^{1}H−^{1}H NMR spectroscopic coupling constants of the C33−C37 portion of the natural product were compared with those of diastereomers **93** and **94**. The large vicinal axial−axial couplings of the C35 methine proton in the phorboxazoles (11.8 Hz) was uniquely correlated with diastereomer **94** (12.0 Hz). The C35 configuration of undesired epimer **93** was easily inverted via a Mitsunobu reaction.[29] Methylation of the C35 alcohol with silver oxide and methyl iodide and subsequent cleavage of the C38 silyl ether gave alcohol **96**. Oxidation of **96** completed the synthesis of NHK coupling partner aldehyde **87**. This synthetic route to access C31−C38 aldehyde **87** was subsequently redesigned to circumvent the inefficient acetoacetate dianion addition as well as the subsequent awkward hydroxyl group functionalizations.

An alternative source of the C37 stereogenic center of the phorboxazoles was L-ascorbic acid.[5b] For this, the C31−C38 aldehyde **87** was prepared from β-hydroxy ester **97**[53] derived from L-ascorbic acid (Scheme 20). Concomitant reduction of

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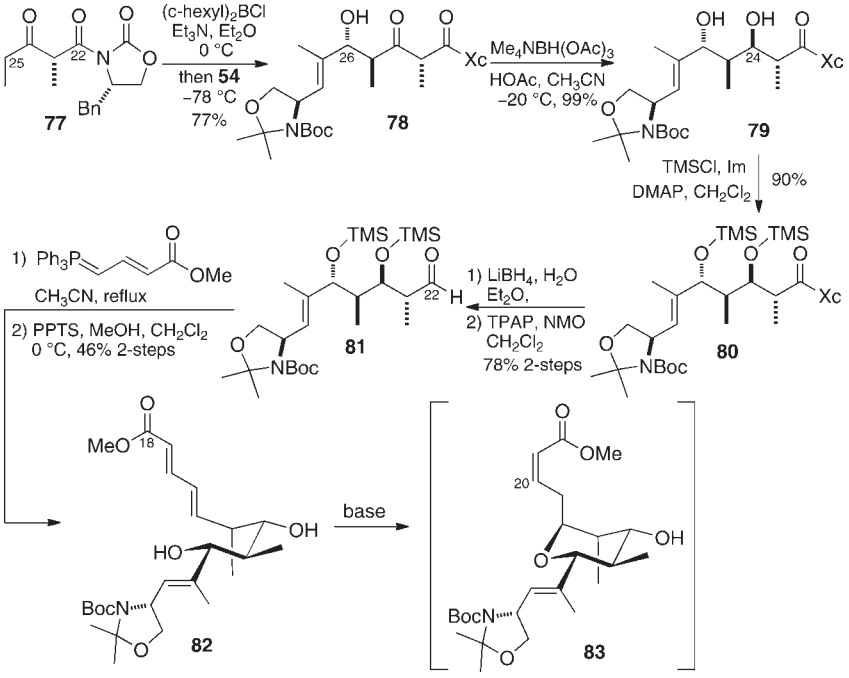
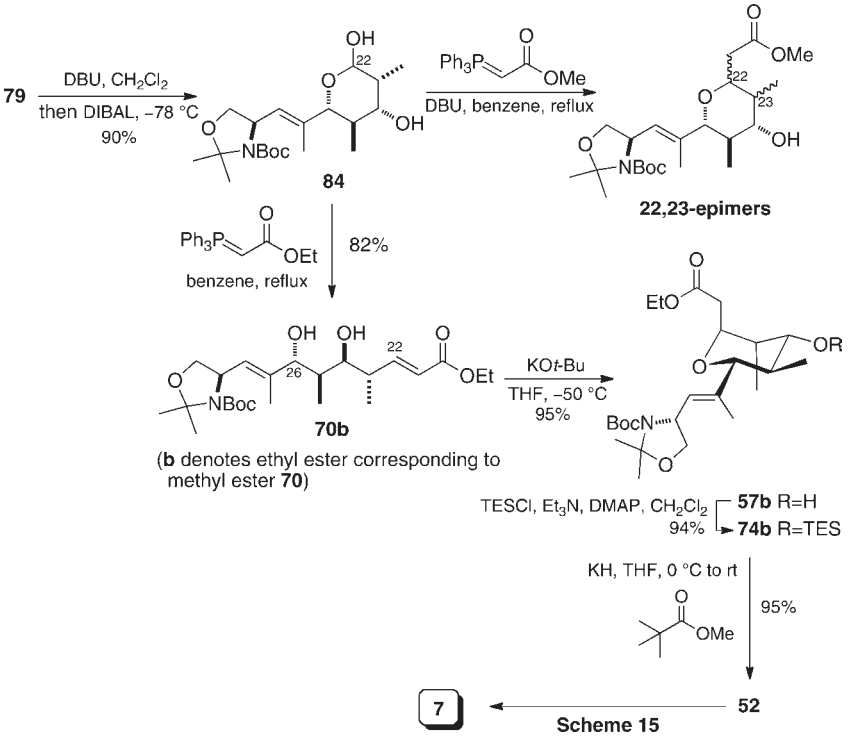
Scheme 16. Attempted 1,6-Addition



Scheme 17. Completion of the Second-Generation Synthesis of the C18−C30 Domain



the ester and β-deoxygenation of **97** could be achieved by a tosylation−$LiAlH_4$ reduction sequence, which provided alcohol **98** in 92% yield. To set the desired C35 configuration, alcohol **98** was oxidized to an aldehyde and then immediately subjected to asymmetric Brown allylation[54] to afford homoallylic alcohol **99** in 70% yield and >95% diastereoselectivity. The generated hydroxyl was methylated using standard conditions (NaH/MeI) to provide the methyl ether **100** in 95% yield. Subsequent ozonolysis of the terminal alkene in **100** led to aldehyde **101**. The C31−C33 β-keto ester moiety was installed in two steps. First, a Reformatsky reaction was performed by treating **101** with methyl bromoacetate and freshly activated zinc powder under

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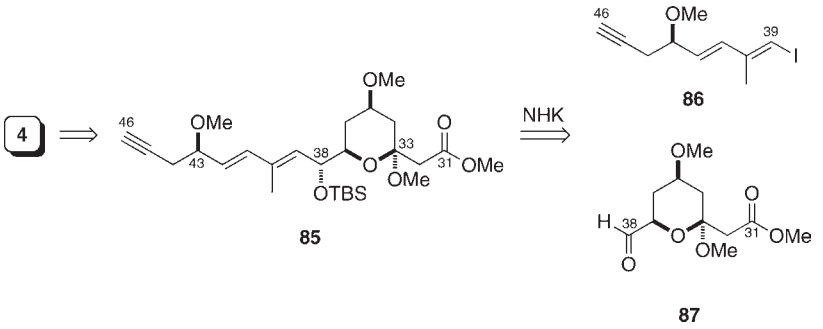
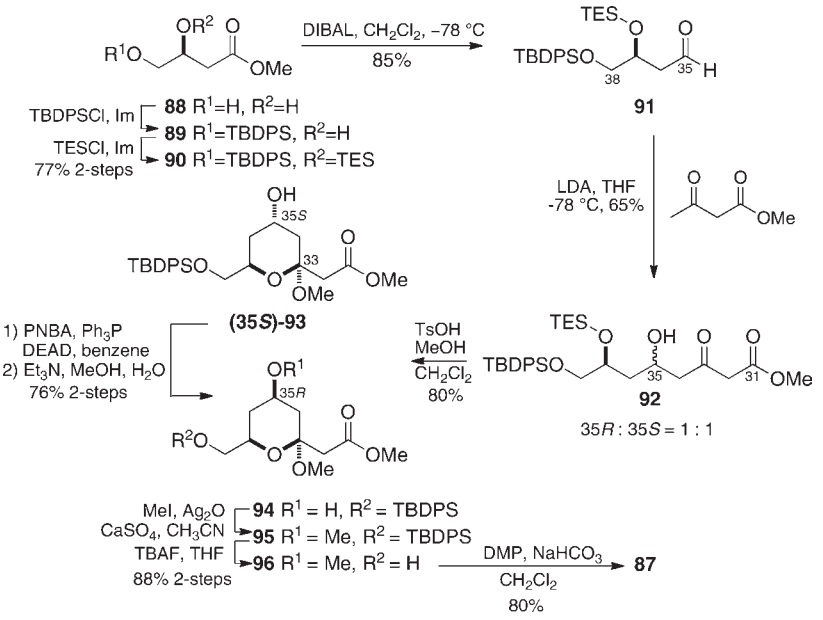
Scheme 18. First-Generation Retrosynthesis of the C31−C46 Domain



Scheme 19. Malic Acid-Derived Synthesis of the C31−C38 Aldehyde 87



ultrasound sonication to furnish the β-hydroxy ester **102** in 75% yield as a 1:1 mixture of alcohol diastereomers. Due to limited success with the oxidation of **102** under Dess−Martin oxidation[47] and Swern conditions,[40] a buffered PCC oxidation[55] was employed to oxidize **102** to β-keto ester **103**. Treatment of **103** with TsOH in methanol and CH_2Cl_2 both cleaved the acetonide moiety and induced ring closure to afford cyclic mixed methyl ketal **96** in 90% yield. Alcohol **96** was then oxidized to give aldehyde **87**. This L-ascorbic acid-based synthetic route provided aldehyde **87** in 22% overall yield in 10 steps from known ester **97**.

The preparation of the C39−C46 coupling partner **86** to complement aldehyde **87** originally began with a methyl metalation of propargyl alcohol using an organoalane−zirconocene complex[56] to generate *E*-vinyl iodide **104** (Scheme 21).[12c,52] An alternative sequence that involved hydroxyl-directed methyl cuprate addition to propargyl alcohol, followed by quenching with iodine, afforded the *Z*-vinyl iodide **105**. Palladium-mediated isomerization of **105** gave **104**.[57] Oxidation of **104** (Dess−Martin periodinane[12c] or TPAP/NMO[52]) gave the known β-iodoaldehyde **106**[58] (Scheme 21). The C42−C45 carbon source was originally derived from 1,3-propanediol as indicated in Scheme 21. This involved a key HWE coupling under Masamune−Roush conditions[41] to yield dieneone **108**. The C43 stereogenic center was then installed via a Corey−Bakshi−Shibata reduction,[59] and the resulting alcohol was methylated using KH/MeI. Desilylation provided primary alcohol **109**. The final carbon was then installed in alkyne **86** via the intermediary aldehyde **106** using dimethyl α-diazomethylphosphonate.[60] This unoptimized route provided useful access to the necessary C39−C46 vinyl iodide.

The design of improved synthetic routes to both C39−C46 vinyl iodide **86** and C31−C38 aldehyde **87** benefited from the use of a C42−C46 sulfone and a 2-deoxy-D-xylose derivative for the C35−C39 fragment that were precedented by Pattenden in their assembly of the C31−C46 domain.[61] The Pattenden sulfone strategy for phorboxazole C39−C42 diene formation has also been employed by Evans[4c] and Williams.[62] Our approach to a streamlined synthesis of vinyl iodide **114**, the C46-trimethysilyl variant of **86**, commenced with the addition of trimethylsilyl lithium acetylide to TBS-protected (*S*)-(−)-glycidol to give alcohol **110** (Scheme 22).[52] Thereafter, efficient methylation of the C43 hydroxyl group was achieved using trimethyloxonium tetrafluoroborate/proton sponge to give the C43 methyl ether **111**. This avoided base-induced silyl migration that occurred

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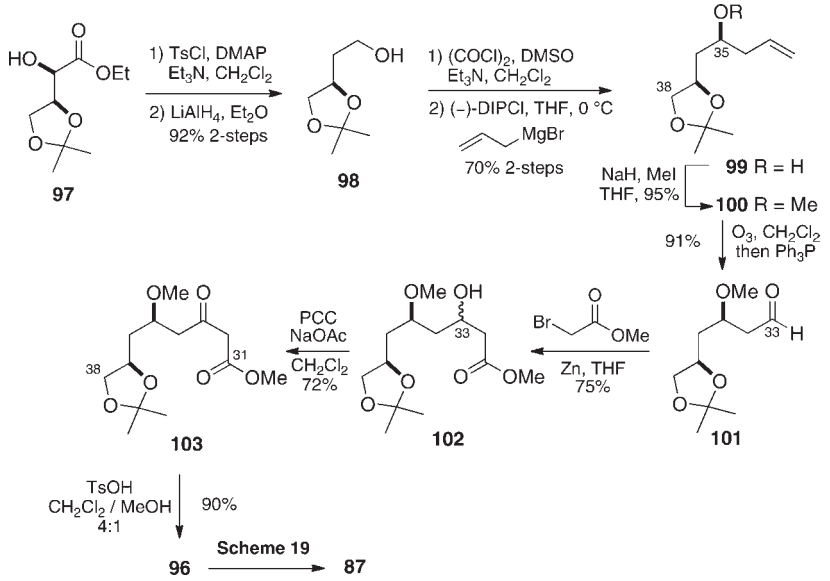
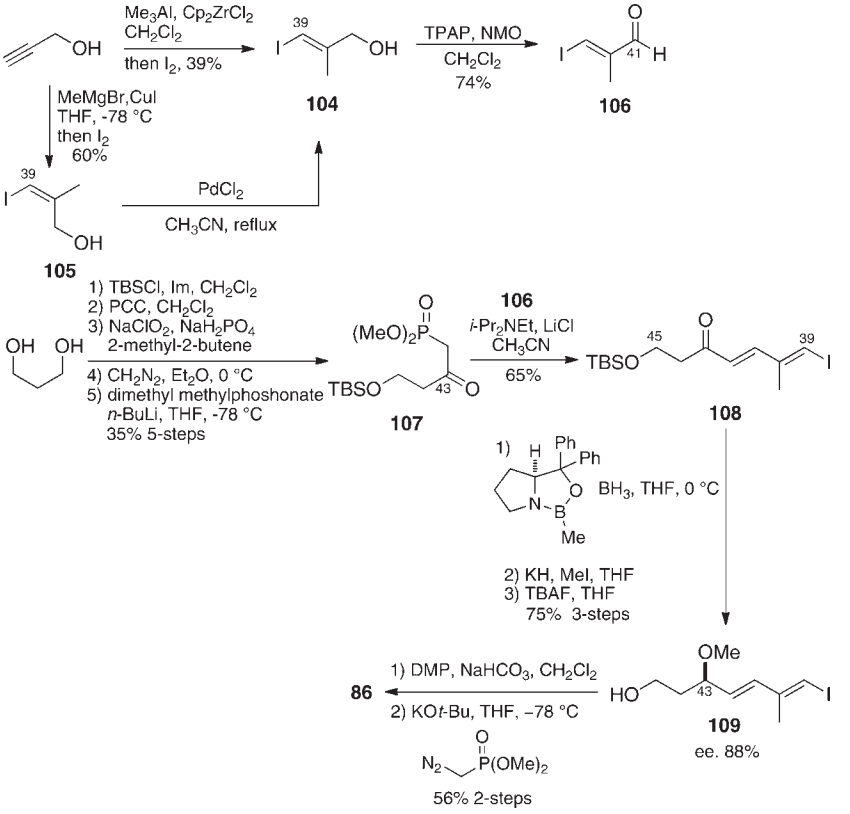
Scheme 20. Ascorbic Acid Route to Aldehyde 87



Scheme 21. Original Synthesis of the C39−C46 Vinyl Iodide 86



using Williamson ether formation conditions for C43 methyl ether formation. Cleavage of the *tert*-butyldimethylsilyl ether of **111** provided primary alcohol **112**, which was converted to sulfone **113** by displacement of the C42 hydroxyl with 2-mercaptobenzothiazole under Mitsunobu reaction conditions[29a] and oxidation of the resulting sulfide. This synthesis of sulfone **113** spanned five steps, with an overall yield of 68% from (*S*)-glycidol-TBS ether.[63] The sulfone **113** underwent olefination[64] with the α,β-unsaturated aldehyde **106** to provide the dienyl iodide **114** in 90% yield and 15:1 *E*:*Z* geometrical selectivity. The vinyl iodide was then employed as a C46-TMS variant of the NHK coupling partner **114** to join the C38 aldehyde **87**.

Organochromium couplings among dienyl iodides **86** and **114** and aldehyde **87** were then surveyed. In the polar aprotic solvent

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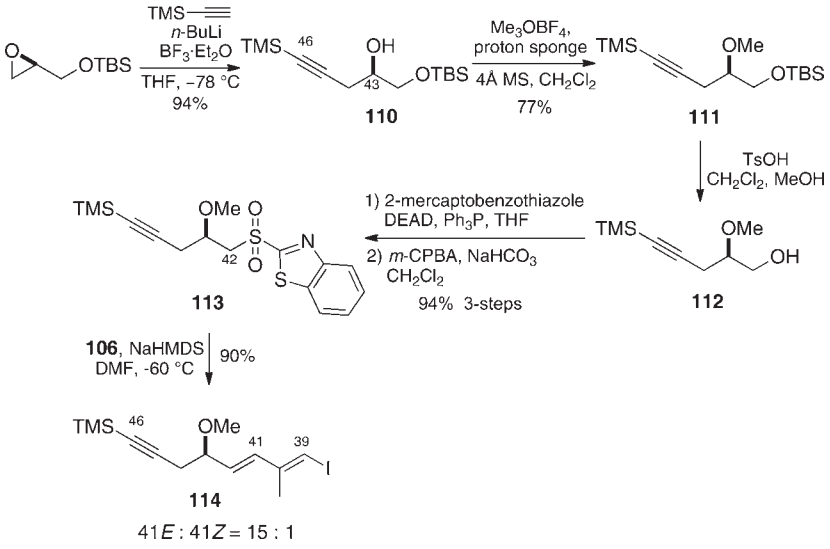
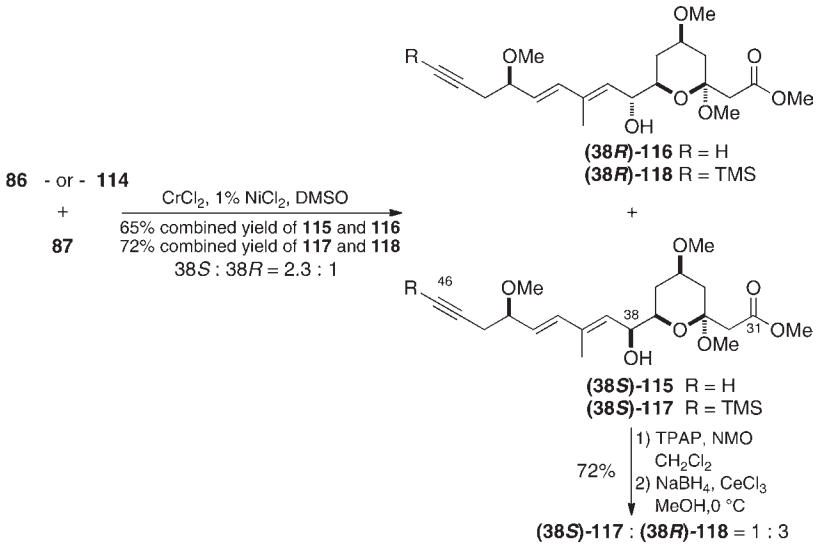
Scheme 22. Abbreviated Synthesis of the C39−C46 Vinyl Iodide 114



Scheme 23. Addition of Dienyl Iodides to Aldehyde 87



DMSO, the NHK couplings predictably gave an excess of the undesired Felkin−Ahn products (Scheme 23). Although the chemoselectivity of this reaction was high, the diastereoselectivity was poor, giving a 2.3:1 ratio of epimeric alcohols, favoring the unnatural (38*S*)-configuration. The terminal silyl substitution of **114** allowed us to survey alternative dienylmetallic species to enhance a chelation-controlled addition to **87**,[4d] but the base sensitivity of ester-aldehyde **87** became limiting. Evans and co-workers obtained a highly stereoselective addition of a C39 vinyl Grignard intermediate to a C38 aldehyde in CH_2Cl_2 near the culmination of their efficient total synthesis phorboxazole B.[4d] As a convenient alternative, the C38 configuration was largely inverted by a simple oxidation/reduction sequence.[52] Thus, compounds **115** and **117** were oxidized with TPAP/NMO to provide ketones which were reduced under Luche conditions[65] to favor the desired (38*R*)-diastereomers **116** or **118** in 3:1 ratios and a combined yield of 72%.

The resultant alcohol **118** was then treated with TBAF to unmask the alkyne, and the C38 hydroxyl was protected as TBS ether **85**. The vinyl bromide moiety was originally installed from terminal alkyne **85** by an AIBN-initiated hydrostannation/bromination sequence, while a low-temperature protocol initiated by triethylborane−air subsequently gave the same result, producing **119** in 70% combined yield.[12c,52] The methyl ester of vinyl bromide **119** was finally saponified to provide the C31−C46 carboxylic acid building block **4** (Scheme 24). This first-generation approach spanned 15 steps from known ester **97** and provided **4** in ca. 3% yield.

3.2. Second-Generation Synthesis of the C31−C46 Domain. The NHK bond formation between the vinyl iodides **86** or **114** and aldehyde **87** allowed for mild reaction conditions that avoided elimination of the C33, C35, or C43 methyl ethers and was chemoselective toward the C38 aldehyde in the presence of the C31 ester. However, the moderate yields and poor diastereoselectivity prompted further refinement. Therefore, an alternative synthesis that incorporates the desired C38 stereocenter early in the synthetic sequence from D-xylose was devel-

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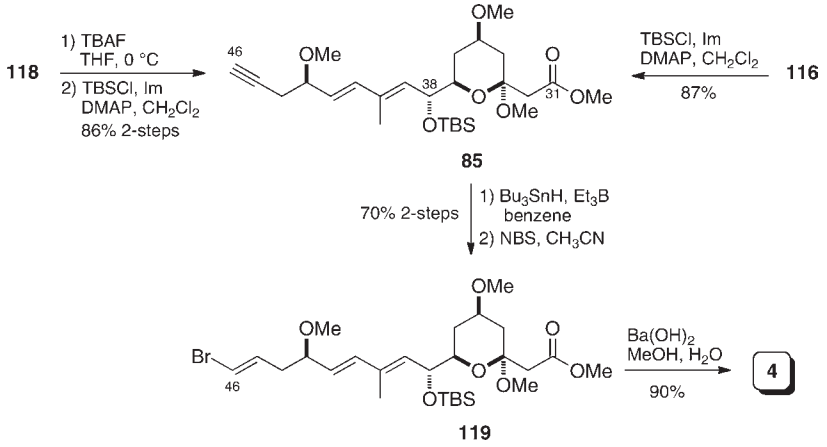
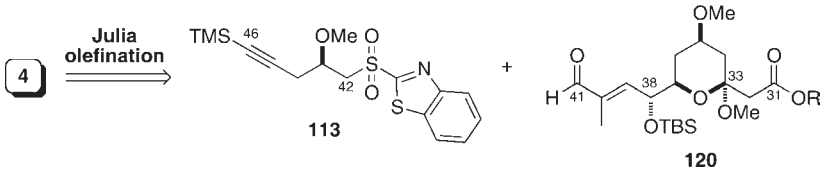
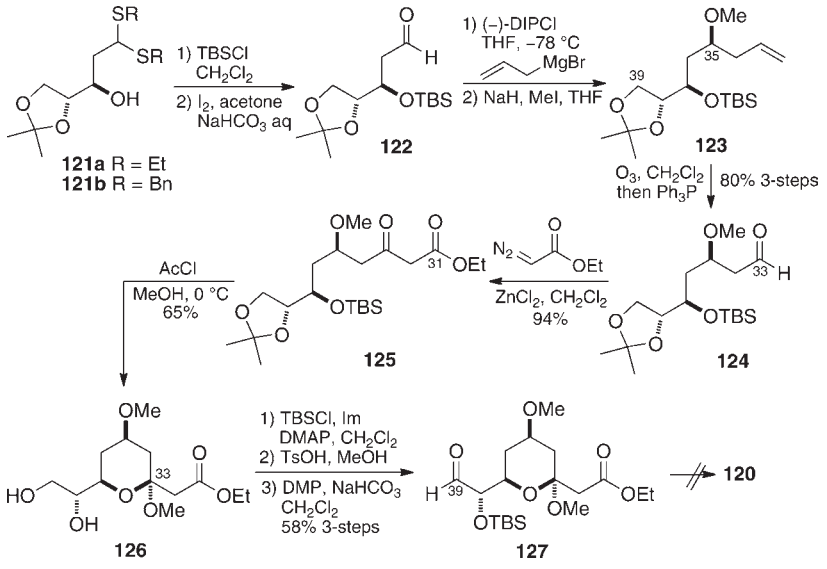
Scheme 24. Completion of the C31−C46 Carboxylic Acid 4



Scheme 25. Julia Olefination-Based Convergent Synthesis of 4



Scheme 26. Attempted Synthesis of the C31−C39 Aldehyde 120



oped. This involved the assembly of **4** based upon the production of the C41−C42 *E*-alkene via convergent coupling of C42−C46 sulfone **4** and C31−C41 conjugated aldehyde **120**, a cylic variant of Pattenden's C33−C38 intermediate[61] (Scheme 25).

Employing a procedure developed by Gray, D-xylose was converted to β-hydroxy-dithioacetal **121a/b** (Scheme 26).[66] The use of the less volatile benzyl thiol in place of ethanethiol made the initial dithioacetalization step less noxious.[67] Protecting the β-hydroxyl and hydrolysis of the thioacetal gave aldehyde **122**. This was then subjected to Brown's asymmetric allylation[54] to generate a homoallylic alcohol. Methylation under basic conditions (MeI/NaH) provided methyl ether **123**. Subjection of alkene **123** to ozonolysis followed by a reductive workup gave aldehyde **124** in 80% yield over three steps. Aldehyde **124** could be converted to β-keto ester **125** via a Reformatsky reaction followed by PCC oxidation[55] in variable yields with difficult product isolation. As an alternative, aldehyde **124** was converted directly to β-keto ester **125** by insertion of the carbene generated from ethyl diazoacetate into the C33 aldehyde (94% yield).[61,68] After an extensive survey, conditions involving *in situ*-generated

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Scheme 27. Optimized Synthesis of the C31−C43 Domain

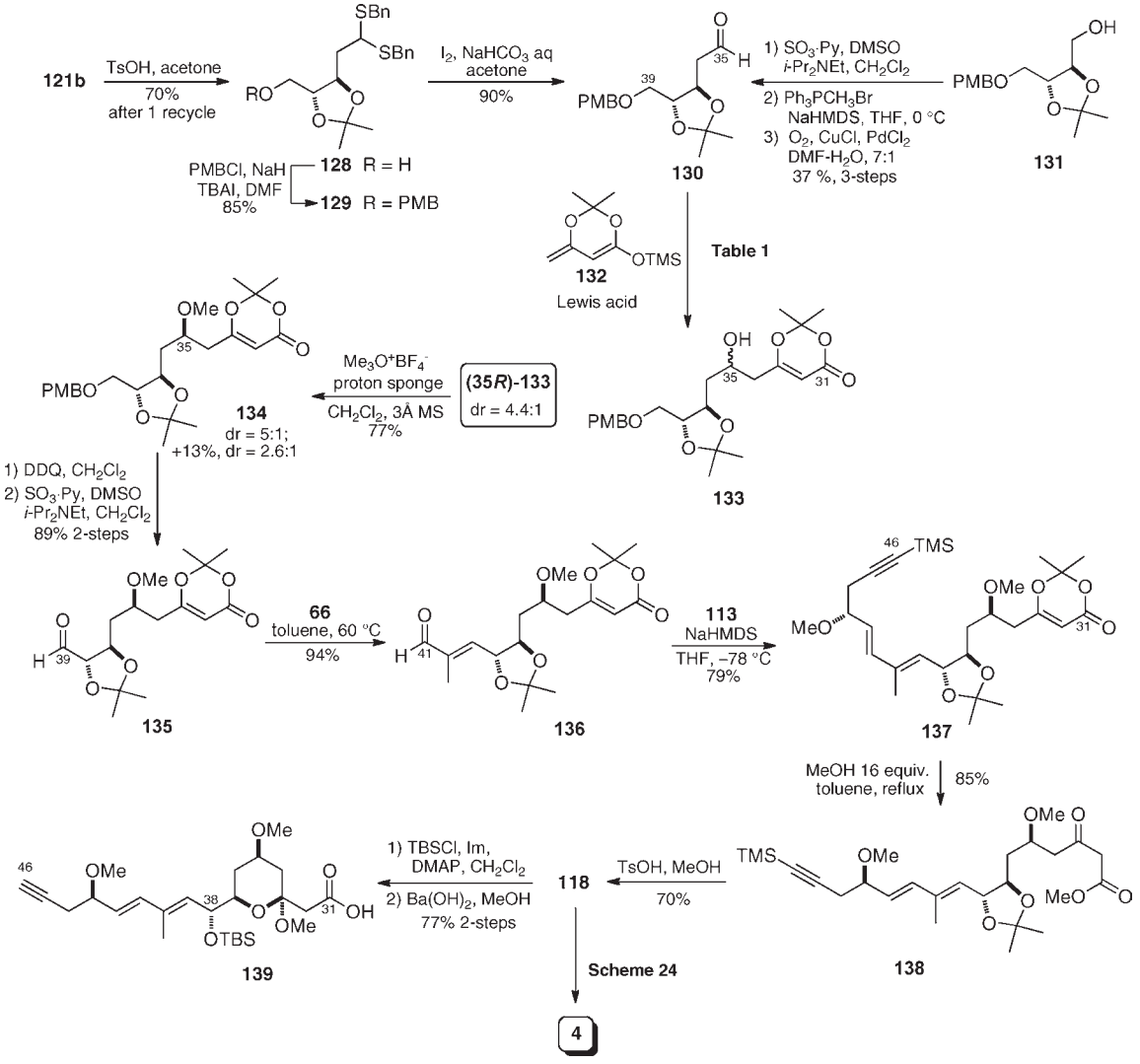

Table 1. Aldol Reaction of Aldehyde 130 and Dienolate 132

entry	Lewis acid	equiv	additive	solvent	combined yield, %	(35*R*)-**133**:(35*S*)-**133**
1	$BF_3 \cdot Et_2O$	1.1−1.5		CH_2Cl_2	50−70	1:1
2	Ti(O*i*-Pr)$_4$ (*S*)-BINOL	0.08	4 Å MS	THF	18	3:1
3	Ti(O*i*-Pr)$_4$ (*S*)-BINOL	0.08−0.10	4 Å MS	toluene	68	1.7:1
4	Ti(O*i*-Pr)$_4$ (*S*)-BINOL	0.08−0.10	4 Å MS *i*-PrOH	toluene	60−66	2.5:1−2:1
5	Ti(O*i*-Pr)$_4$ (*S*)-Carreira's ligand	0.05		Et_2O	14−21	2:1
6	Ti(O*i*-Pr)$_4$ (*S*)-Carreira's ligand	0.065		toluene	81	2.5:1
7	Ti(O*i*-Pr)$_2Cl_2$	1.2		CH_2Cl_2	80	2.5:1
8	Ti(O*i*-Pr)$_2Cl_2$	1.2		toluene	90	4.4:1

HCl in methanol at 0 °C were found to best trigger the removal of the acetonide and TBS protecting groups from **125** and lead to ketalization to afford cyclic mixed methyl ketal **126** in 65% yield.

Protection of diol **126** as its bis-silyl ether, followed by selective cleavage of the C39 silyl ether, provided a primary alcohol, which was oxidized to aldehyde **127**. At this juncture, all attempts to

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homologate **127** to conjugated aldehyde **120** via Wittig reaction with (1-formyl)ethylidene-triphenylphosphorane **66**[43] (Scheme 13) were unsuccessful. The C38-OTES analogue of **127** was also inert under the same reaction conditions. Although reaction of **127** with (1-ethoxycarbonyl)ethylidene-triphenylphosphorane **65**[42] (Scheme 13) gave the homologated conjugated ester, the differentiation of the two ester termini of the product was tedious.[69] Therefore, assembly of the C31−C46 domain in a more linear sequence via a late-stage closure of the C33−C37 oxane ring was pursued.

The optimized synthetic route to the phorboxazole C31−C46 domain is illustrated in Scheme 27. This utilized the 1°,2°-acetonide **121b**[67] derived from D-xylose as the source of the phorboxazole C37 and C38 stereogenic centers. The acetonide protecting group could be isomerized to the thermodynamically preferred 2°,2°-acetonide **128**, by analogy to a similar transformation reported by Roush.[70] The primary alcohol was converted into PMB ether **129** before dispensing of the dithiolacetal to reveal aldehyde **130**. An alternative preparation of **130** exploited the tartrate derivative **131**,[71] the free alcohol of which was converted into the one-carbon-homoligated aldehyde **130** via a regioselective Wacker oxidation of an intermediate terminal alkene. This gave aldehyde **130** in 66% yield, along with 7% of the methyl ketone.[72]

A variety of Lewis acids and reaction conditions were surveyed for the catalytic asymmetric addition of the acetoacetate dienolate equivalent **132**[73] to aldehyde **130** (Scheme 27, Table 1). The yields and levels of diastereoselectivity were poor to modest in most cases, including those using Ti(O*i*-Pr)$_4$/(*S*)-BINOL (entries 2−4)[74] and Ti(O*i*-Pr)$_4$/(*S*)-Carreira's ligand (entries 5 and 6).[75] These results may reflect mismatched diastereoselection arising from the resident chirality in **130**. In fact, the best results were obtained with a stoichiometric excess of Ti(O*i*-Pr)$_2$Cl$_2$ and *the absence* of any chiral ligands (entry 8), which gave a 4.4:1.0 ratio of (35*R*)-**133**:(35*S*)-**133** in 90% combined yield (73% direct yield of the desired (35*R*)-isomer). This compares favorably with the direct acetoacetate dianion addition upon malic acid-derived aldehyde **91**, which gave the epimeric C35 alcohols **92** in a 1:1 ratio and 65% combined yield (Scheme 19).

The C35 epimers of **133** co-chromatographed and were not entirely separated until after cyclization to mixed ketals **118** (Scheme 27). Prior to that, slight kinetic enrichment of the diastereomeric ratio was achieved via methyl ether formation using Meerwein's reagent trimethyloxonium tetrafluororoborate and proton sponge. This gave methyl ether **134** in 77% yield and 5:1 dr, favoring the desired (35*R*)-isomer. Resubjection of the unreacted alcohols **133** to the methylation conditions afforded an additional 13% of **134** in 2.6:1 dr. Next, the PMB ether was converted into aldehyde **135** in two steps. Homologation of **135** using phosphorane **66**[43] (Scheme 13) gave α,β-unsaturated aldehyde **136** in high yield and *E*-selectivity. Condensation of **136** with the C42−C46 sulfone **113** provided (39*E*,41*E*)-diene **137** in 79% yield. Thermal cycloreversion in the presence of methanol ejected acetone from **137** to form β-keto ester **138**. Acidic methanolysis then removed the acetonide protecting group and trapped the C33 ketone as mixed methyl ketal **118** in 70% combined yield for (35*R*)-**118**. The desired (35*R*)-diastereomer was then converted into either the terminal alkyne **139** or vinyl bromide **4**.

The third and final essential building block **4** for the phorboxazole total synthesis via convergent oxazole formations was thus completed (Scheme 27) in ca. 6% yield from the known 2-deoxy-D-xylose derivative **121b** over 16 steps, or in ca. 11% yield from tartrate derivative **130** in 13 steps (*ent*-**130** has previously been reported[72]). This building block synthesis is highlighted by the elaboration of **121b** involving a moderately stereoselective substrate-based acetoacetate dianion equivalent addition and subsequent Julia olefination.[64] Three advantages to targeting the synthesis of the corresponding terminal C31−C46 terminal alkyne **139** are that it is somewhat simpler to access than the vinyl bromide, the full-length analogue 45,46-dehydrobromo-phorboxazole A into which **139** has been incorporated appears to retain a level and spectrum of biological activities similar to those of **1**,[6] and the alkyne provides a useful handle for terminal functionalization, e.g., via Sonogashira couplings.[8] This versatile fragment **139** was obtained in ca. 8% yield from **121b** over 13 steps (ca. 15% from **130** in 10 steps).

CONCLUSION

As a result of continuing efforts, we have developed efficient syntheses of our originally reported phorboxazole building blocks. This is highlighted by the synthetic utility of an iterative hetero-Diels−Alder assembly of the C3−C17 domain **6** (cf. Schemes 9 and 10), a hetero-Michael addition/equilibration process to stereoselectively form the central oxane-containing C18−C30 intermediate **7** (cf. Schemes 16 and 17), and a convergent chiral-pool-based assembly of the C31−C46 side-chain domain **4** (Scheme 27). Each major fragment was prepared in a scalable fashion using the optimized routes. This includes the preparation of each in 13 or fewer steps and ≥11% overall yield in the longest linear sequence, with the synthesis of the C31−C46 domain being the lengthiest. Importantly, each fragment bears terminal functionalization that may be readily used for convergent fragment couplings to generate phorboxazole A and its analogues.[76]

ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for compounds **4**, **6**, **7**, **9**, **46**, **48**, **49**−**52**, **57b**, **70b**, **74b**, **75**, **78**, **79**, **84**, **85**, **87**, **96**, **99**−**103**, **110**, **111**, **113**, **114**, **118**, **128**−**130**, **133**, **134**, and **136**−**139**, including ^{1}H and ^{13}C NMR spectra of key compounds and CIF files for compounds **29**, **46**, and **57**. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) Schwarzer, D.; Finking, R.; Marahiel, M. A. *Nat. Prod. Rep.* **2003**, *20*, 275–287.

(2) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995,** *117,* 8126–8131. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996,** *118,* 9422–9423. (c) Molinski, T. F. *Tetrahedron Lett.* **1996,** *37,* 7879–7980.

(3) Capon, R. J.; Skene, C.; Liu, E. H.; Lacey, E.; Gill, J. H.; Heilan, K.; Friedel, T. *Nat. Prod. Res.* **2004,** *18,* 305–309.

(4) (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998,** *120,* 5597–5598. (b) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000,** *39,* 2533–2536. (c) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000,** *39,* 2536–2540. (d) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000,** *122,* 10033–10046. (e) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001,** *123,* 4834–4836. (f) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001,** *123,* 10942–10953. (g) González, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003,** *42,* 1255–1258. (h) Pattenden, G. González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003,** *1,* 4173–4208. (i) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003,** *42,* 1258–1262. (j) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 12058–12063. (k) Li, D.; Zhang, D.; Sun, C.; Zhang, J.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.; Lin, G. *Chem.—Eur. J.* **2006,** *12,* 1185–1204. (l) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006,** *8,* 6039–6042. (m) White, J. D.; Lee, T. H.; Kunttiyong, P. *Org. Lett.* **2006,** *8,* 6043–6046. (n) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007,** *46,* 7 69–772. (o) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005,** *7,* 4399–4402. (p) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T.; Meis, R. M. *J. Org. Chem.* **2008,** *73,* 1192–1200.

(5) (a) Lee, C. S. Ph.D. Thesis, University of Minnesota, 1999. (b) Hansen, T. M. Ph.D. Thesis, University of Minnesota, 2002.

(6) Uckun, F. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2001,** *11,* 1181–1183.

(7) (a) Smith, A. B., III; Razler, T. M.; Pettit, G. R.; Chapuis, J. *Org. Lett.* **2005,** *7,* 4403–4406. (b) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *Org. Lett.* **2006,** *8,* 797–799. (c) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *J. Org. Chem.* **2008,** *73,* 1201–1208 and references therein.

(8) (a) Hansen, T. M.; Engler, M. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2003,** *13,* 2127–2130. (b) Chen, J.; Ying, L.; Hansen, T. M.; Engler, M. M.; Lee, C. S.; La Clair, J. J.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2006,** *16,* 901–904. (c) Forsyth, C. J.; Chen, J.; Ying, L.; La Clair, J. *J. Am. Chem. Soc.* **2006,** *128,* 3858–3859.

(9) (a) Crimmin, M. J.; O'Hanlon, P. J.; Rogers, N. H.; Sime, F. M.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1989,** 2059.

(10) (a) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993,** *58,* 3604–3606. (b) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995,** *117,* 558–559.

(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983,** *24,* 4405–4408.

(12) (a) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997,** *62,* 5672–5673. (b) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996,** *37,* 6449–6452. (c) Ahmed, F.; Forsyth, C. J. *Tetrahedron Lett.* **1998,** *39,* 183–186.

(13) (a) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986,** *51,* 2609–2612; (b) Garner, P.; Park, J. M. *Org. Synth.* **1998,** *Coll. Vol. 9,* 300; **1992,** *70,* 18.

(14) (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991,** *30,* 1531–1546. (b) Reetz, M. T.; Schmitz, A.; Holdgrun, X. *Tetrahedron Lett.* **1989,** *30,* 5421–5424.

(15) Cink, R. D. Ph.D. Thesis, University of Minnesota, 1998.

(16) Mujica, M. T.; Afonso, M. M.; Galindo, A.; Palenzuela, J. A. *Tetrahedron* **1996,** *52,* 2167–2176.

(17) These results, disclosed in 1998,[15] were recently replicated: Fontana, C.; Incerti, M.; Moyna, G.; Manta, E. *Tetrahedron: Asymmetry* **2010,** *21,* 398–404.

(18) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *J. Org. Chem.* **1982,** *47,* 1981–1983.

(19) Chen, J. Ph.D. Thesis, University of Minnesota, 2004.

(20) Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973,** *3,* 67–72.

(21) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991,** *32,* 4665–4668.

(22) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, T.; Uchimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986,** *108,* 6048–6050. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986,** *108,* 5644–5646. (c) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977,** *99,* 3179–3181.

(23) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976,** 1295–1298.

(24) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984,** *25,* 265–268.

(25) (a) Mori, K.; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979,** *35,* 933–940. (b) Hanessian, S.; Ugolini, A.; Dube, D.; Glamyan, A. *Can. J. Chem.* **1984,** *62,* 2146–2149.

(26) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1995,** *60,* 8122–8123.

(27) (a) Trost, B. M.; Coppola, B. P. *J. Am. Chem. Soc.* **1982,** *104,* 6879–6881. (b) Trost, B. M.; Buch, M.; Miller, M. L. *J. Org. Chem.* **1988,** *53,* 4887–4888.

(28) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969,** *34,* 2543–2549. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973,** *95,* 512–519. (c) Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973,** *38,* 2143–2147.

(29) (a) Mitsunobu, O. *Synthesis* **1981,** *1,* 28. (b) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991,** *32,* 3017–3020.

(30) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. J. *Tetrahedron Lett.* **1977,** 1977–1980.

(31) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983,** *24,* 763–764.

(32) Garner, P.; Yoo, J. U.; Sarabu, R.; Kennedy, V. O.; Youngs, W. J. *Tetrahedron* **1998,** *54,* 9303–9316.

(33) Lu, Y. M.S. Thesis, University of Minnesota, 2003.

(34) Diene **45** was prepared in 87% from 3-(*p*-methoxylbenzyloxy)-propanal in two steps. See Supporting Information.

(35) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989,** *30,* 7121–7124.

(36) Evans, D. A.; Chapman, K. T.; Carreria, E. M. *J. Am. Chem. Soc.* **1988,** *110,* 3560–3578.

(37) Betancort, J. M.; Martin, V. S.; Padron, J. M.; Palazon, J. M.; Ramirez, M. A.; Soler, M. A. *J. Org. Chem.* **1997,** *62,* 4584–4590.

(38) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996,** 967–969.

(39) (a) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985,** 2247–2250. (b) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988,** *29,* 4139–4142.

(40) (a) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976,** *41,* 3329–3331. (b) Omura, K.; Swern, D. *Tetrahedron* **1978,** *34,* 1651–1660.

(41) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984,** *25,* 2183–2186.

(42) Isher, O.; Gutmann, M.; Montavon, M.; Riiegg, R.; Ryser, G.; Zeller, P. *Helv. Chim. Acta* **1957,** *139,* 1242–1249.

(43) (a) Schlessinger, R. H.; Pross, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985,** *26,* 2391–2394. (b) Trippet, S.; Walker, D. M. *J. Chem. Soc.* **1961,** 1266–1272.

(44) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989,** *111,* 3441–3442.

(45) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982,** *23,* 885–888. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986,** *42,* 3021–3028.

(46) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994,** 639–666.

(47) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983,** *48,* 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991,** *113,* 7277–7287.

(48) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984,** *106,* 1154–1156.

(49) Kim, S.-K.; Hatori, M.; Ojika, M.; Sakagami, Y.; Marumo, S. *Bioorg. Med. Chem. Lett.* **1998,** *6,* 1975–1982.

(50) Fürstner, A. *Chem. Rev.* **1999,** *99,* 991–1046.

(51) Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992,** *40*, 4067–4086.
(52) Ahmed, F. Ph.D. Thesis, University of Minnesota, 1999.
(53) Abushanab, E.; Vemishetti, P.; Leiby, R. W.; Singh, H. K.; Mikkilineni, A. B.; Wu, D. C. J.; Saibaba, R.; Panzica, R. P. *J. Org. Chem.* **1988,** *53*, 2598–2602.
(54) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986,** *51*, 432–439.
(55) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975,** *16*, 2647–2650.
(56) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981,** *46*, 4093–4096.
(57) (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979,** *168*, 1–11. (b) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979,** *168*, 227–232.
(58) Baker, R.; Castro, J. L. *J. Chem. Soc., Perkin Trans. I* **1990,** 47–65.
(59) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988,** *53*, 2861–2863.
(60) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971,** *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982,** *47*, 1837–1845.
(61) Pattenden, G.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Tetrahedron Lett.* **1998,** *39*, 6099–6102.
(62) Williams, D. R.; Clark, M. P.; Emde, U.; Berliner, M. A. *Org. Lett.* **2000,** *2*, 3032–3026.
(63) Compounds **112** and **113** were previously prepared by Pattenden.[61]
(64) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991,** *32*, 1175–1178.
(65) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978,** *100*, 2226–2227. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981,** *103*, 5454–5459.
(66) Gray, G. R.; Wong, M. Y. H. *J. Am. Chem. Soc.* **1978,** *100*, 3548–3553.
(67) See Supporting Information.
(68) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989,** *54*, 3258–3260.
(69) Engler, M. M. Ph.D. Thesis , University of Minnesota, 2004.
(70) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989,** *54*, 915–930.
(71) Ono, M.; Nishimura, K.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **2001,** *66*, 8199–8203.
(72) The entantiomer of **130** was previously synthesized from the corresponding alkene via Wacker oxidation in 93% yield: Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H *J. Org. Chem.* **1995,** *60*, 4678–4679. However, we did not achieve the same levels of yield and regioselectivity.
(73) Sato, M.; Sugita, Y.; Abiko, Y.; Kaneko, C. *Tetrahedron: Asymmetry* **1992,** *3*, 1157–1160.
(74) Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. *Heterocycles* **1995,** *41*, 1435–1444.
(75) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003,** *68*, 9274–9283.
(76) Wang, B.; Hansen, T. M.; Weyer, L.; Wu, D.; Wang, T.; Christmann, M.; Lu, Y.; Ying, L.; Engler, M. M.; Cink, R. D.; Lee, C. S.; Ahmed, F.; Forsyth, C. J. *J. Am. Chem. Soc.* **2011,** *133*, http://dx.doi.org/10.1021/ja1089099.